The British Journal of Surgery

Volume 74, Number 5, May 1987

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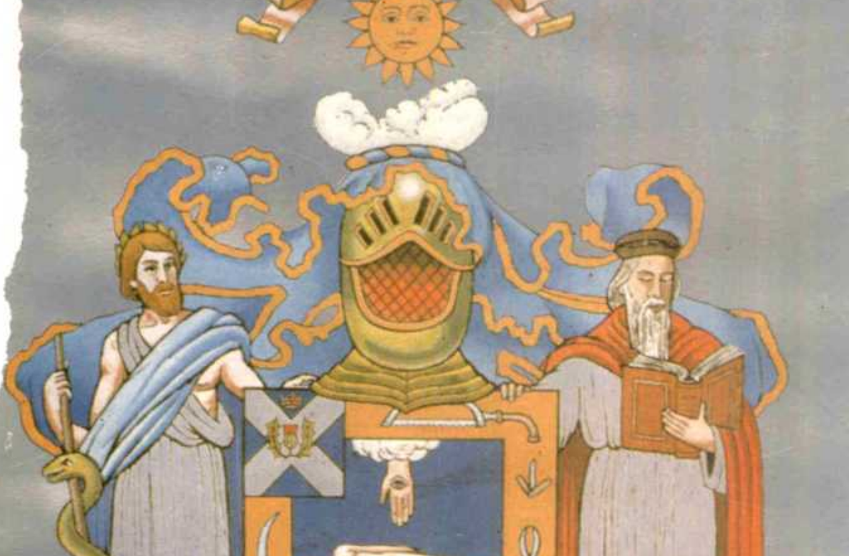

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Abbreviated prescribing information
Dosage *Adults:* Generally 750mg t.i.d. i.m. or i.v. Severe infections 1·5g t.i.d. i.v. Frequency of injections can be increased to 6-hourly if necessary. *Infants and children:* 30 to 100mg/kg/day in 3 or 4 divided doses. 60mg/kg/day will be appropriate for most infections. *Neonates:* 30 to 100mg/kg/day in 2 or 3 divided doses. *Gonorrhoea:* Single dose of 1·5g (2 x 750mg into different sites). *Prophylaxis:* The usual dose of 1·5g i.v. with induction of anaesthesia for abdominal, pelvic and orthopaedic operations, may be supplemented with two 750mg i.m. doses 8 and 16 hours later. In cardiac, pulmonary, oesophageal and vascular operations, the usual dose is 1·5g i.v. with induction of anaesthesia continuing with 750mg i.m. t.i.d. for a further 24 to 48 hours. In total joint replacement, 1·5g cefuroxime powder may be mixed dry with each pack of methyl methacrylate cement polymer before adding the liquid monomer.
Contra-indication Hypersensitivity to cephalosporins.
Precautions Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins. Care is indicated in patients who have experienced an anaphylactic reaction to penicillin. As with all drugs, Zinacef should be administered with caution during the early months of pregnancy. Zinacef should not be mixed in the syringe with aminoglycoside antibiotics. Reduce dosage when renal function is markedly impaired. (See Data Sheet for details). Cephalosporins at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as frusemide, as these combinations are suspected of adversely affecting renal function. Clinical experience with Zinacef has shown that this is not likely to be a problem at the recommended dose levels.
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Filmset by Mid-County Press, London SW15. Printed by The Friary Press Ltd, Dorchester and London.

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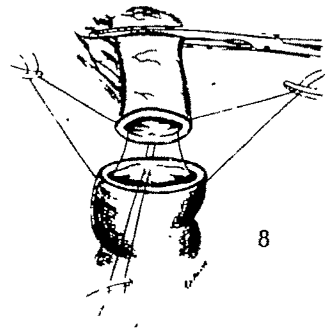
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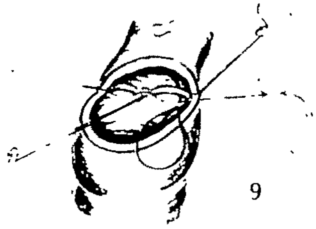
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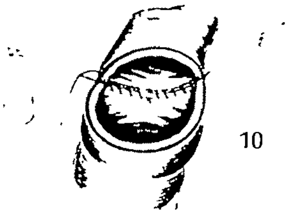
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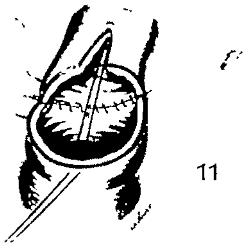
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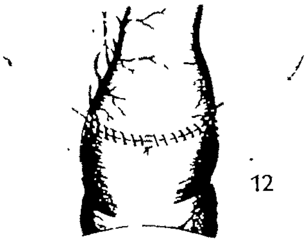
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ISSN 0007-1323

Filmset by Mid-County Press, London SW15. Printed by The Friary Press Ltd, Dorchester and London.

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The British Journal of Surgery

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The British Journal of Surgery is published monthly by Butterworth Scientific Limited, PO Box 63, Westbury House, Bury Street, Guildford GU2 5BH, UK. Telephone: 0483 300966. Telegrams and Telex 859556 SCITEC G. Registered office: Butterworth Scientific Limited, 88 Kingsway, London WC2 6AB, UK.

Publisher: Charles Fry
Executive Editor: Sarah Graham-Campbell
Sub-Editors: June Greig-Smith
Helen Juden
Production: Nick Wilson
Advertisement Sales Representative: Mark Butler

UK and Overseas subscription orders should be sent to: Westbury Subscription Services, P.O. Box 101, Sevenoaks, Kent TN15 8PL, UK. Telephone: 0732-885833. Telex: 95678. Facsimile: 0732–884079. Cable: Westbury, Sevenoaks, Kent. North American orders should be sent to: Journals Fulfilment Department, Butterworths, 80 Montvale Avenue, Stoneham, MA 02180, USA. Telex: 880052. Telephone: (617) 438 8464.

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ISSN 0007-1323

Filmset by Mid-County Press, London SW15. Printed by The Friary Press Ltd, Dorchester and London.

Br. J. Surg. 1987, Vol. 74, May, 339–340

Liver transplantation: a subtle revolution

The recent publication by Kirby and colleagues in this journal (*Br J Surg* 1987; **74**: 3–11) comes at a time when we are witnessing an undoubted expansion in liver transplantation. Whereas 568 transplants were performed in the United States up until 1984[1], 602 were undertaken in 1985, 250 of these by Starzl's group in Pittsburgh. In Europe, 1300 patients have been transplanted to date, many of them in the last 2 years[2]. These numbers have affirmed the belief of the NIH Consensus Development Conference of June 1983[3] which declared that liver transplantation '...deserves broader application'. Seventy centres (40 in USA, 30 in Europe) have now joined the pioneering teams of Starzl, Calne in Cambridge and Pilchmayr in Hanover. The reasons for this enthusiasm are evident from the general experience of the various centres with one year survival of about 70 per cent for adults and 80 per cent or more for children. In my own institution, 78 liver transplantations have been undertaken in the elective programme which commenced in December 1984 (excluding emergency transplants in fulminant hepatic failure) with a 2 year survival of 85 per cent. All the deaths have occurred in the first 6 months and the quality of life for survivors has been remarkably good.

One of the most surprising features of these improved results has been that the techniques of orthotopic transplantation used in the early days have altered little. The only operative change has been in the type of biliary enteric anastomosis which is associated now with less risk than the early cholecystoduodenal anastomosis. The use of an extracorporeal pump during hepatectomy[4] in the cirrhotic patient is a recent technical improvement which decreases peroperative bleeding and avoids the deleterious effect on renal function seen with caval clamping. This, in turn, has allowed earlier use of potentially nephrotoxic immunosuppressants such as cyclosporin. It seems unlikely that this recent change in technique has been responsible for the improved results since it is not used in all centres. Similarly, the methods of cooling and preservation following harvest of the donor liver have not altered over the last 20 years. Two factors can be held responsible for the increased duration of survival. The first is the introduction of cyclosporin A which has diminished the complications previously associated with the use of large doses of corticosteroids. The second, which I believe is more significant, is the change in indications for liver transplantation. Before 1984, the vast majority of referred patients had a life expectancy measurable in weeks or months. At the present time we continue to offer transplantation to some of these ill patients but make every attempt to ameliorate their condition before intervention. We no longer operate on moribund patients with cachexia, jaundice, renal dysfunction and encephalopathy for past experience has shown that, if these patients are fortunate enough to survive surgery, there is a high risk of their succumbing to a variety of post-operative complications[5]. It was undoubtedly the poor results obtained in such patients that were responsible for the slowing down of many transplant programmes before the 1980s. Since then, all our efforts have been put into transplanting the same patients but at an earlier stage of their disease process.

There is now a general consensus of opinion on the liver diseases meriting transplantation and this is well covered in the paper from Birmingham. Primary biliary cirrhosis is a disease which pursues a predictable course and transplantation can be planned and undertaken before hepatocellular insufficiency is too far advanced. In sclerosing cholangitis, the clinical picture of a symptomatic patient with diffuse intrahepatic lesions is a prime indication for liver transplantation. The symptoms arising as a result of cholestasis in these groups of patients are in themselves a strong indication for intervention before hepatic insufficiency has developed. However, these are rare patients and one can ask why transplantation has not been proposed more frequently in the common cirrhotic conditions. Our experience with alcoholic associated liver disease, which is a commonly found condition in France, exemplifies

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Acknowledgement: I would like to acknowledge the help of Mr O. James Garden in the preparation of this manuscript

0007–1323/87/050339–02$3.00

the problem. Although we do not consider an alcohol aetiology a contra-indication in itself, few patients are submitted to our programme because of advanced age, continued alcohol abuse or poor motivation. It is possible that posthepatic cirrhosis could become the most common indication for liver transplantation since younger individuals are often affected. Unfortunately, this disease does not follow a predictable course and it is difficult at present to envisage a transplant in a patient whose prospects of survival appear good but who may quickly succumb to a sudden complication such as infection and/or gastrointestinal haemorrhage. It should also be appreciated that liver transplantation in this group of patients is technically more difficult and there remains the uncertainty of the viral effect on the donor liver. Transplantation for primary liver cancer is one of the indications where the demands on the patient, family and clinician are often greatest. It is in this group that the long-term results for transplantation are poorest due to the appearance of recurrent disease. For this reason, liver transplantation is only envisaged by our team when disease appears to be confined to the liver. If there is doubt, it is our practice to undertake an exploratory laparotomy before a patient is accepted for transplant. Even at the time of transplant, we undertake repeated histological examinations during hepatic dissection to exclude the presence of extrahepatic tumour which, if found, aborts transplantation.

The improved results of liver transplantation are in the process of altering the management of the chronic liver diseases, since the clinician now has to bear in mind that the patient may be offered transplantation in the future to treat exacerbation of the liver disease. When haemorrhage occurs in a portal hypertension patient, the clinician should remember that any abdominal operation on the oesophagus or attempted portal decompression will subsequently increase the technical difficulties of transplantation. Sclerotherapy is the least invasive treatment of variceal haemorrhage but, if portal decompression cannot be avoided, a mesentericocaval shunt seems the best surgical option since it does not involve surgery in the supracolic compartment and can be easily reversed at the time of transplantation.

The appearance of ascites or variceal haemorrhage in a patient with established liver disease may lead the clinician to consider liver transplantation although other factors such as age should be taken into account. Even when complications do not develop, transplantation may be considered at the first surgical procedure for diseases such as sclerosing cholangitis. These changes in therapeutic approach raise the question of which surgeon is best qualified to treat the patient at the outset of his or her illness. One can foresee the day when a trained hepatobiliary surgeon could provide a range of therapeutic options from simple biliary or hepatic procedures to liver transplantation. I believe that the broader application of liver transplantation as a treatment for severe liver disease will be a driving force in the development of such specialists and that the rise in the number of foreseeable transplantations will contribute greatly to this evolution. It is just possible to estimate the total number of transplants that will be undertaken across the world, if only patients with primary biliary cirrhosis, sclerosing cholangitis, biliary atresia and other rare conditions are considered but it is almost impossible to do so when the common causes of cirrhosis are taken into account. It seems certain that the application of less strict criteria when considering this latter group for transplantation will lead to a vast increase in the numbers entered into transplant programmes in the future.

We are without doubt at the beginning of a revolution which is unlikely to be explosive owing to the limitations imposed by technical problems and organizational difficulties. However, with the pressure of the demands of motivated patients and informed doctors, it will be difficult not to offer to patients with fatal liver disease the only radical therapeutic option, namely liver transplantation.

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Br. J. Surg. 1987, Vol. 74, May, 341–342

In the BJS now

The Editorial Committee of our Journal meets three times a year. There is much routine business: how do we make it worthwhile for our editors to be so devoted to the Journal; what is the next advance in computerization of the editorial office; are we falling behind in publishing overseas papers; are we falling behind? Yet often and often the subject returns to the question of what sort of Journal are we or do we want to be? At our founding in 1914 we were not only representative of a British tradition of surgical endeavour but also a *general* journal.

As everyone knows things have changed; if there is any theme running through 20th century surgery it is the emergence of technical specialization. Time was, when as a senior registrar in general surgery, one of us would boast of 105 consecutive transvesical prostatectomies as emergencies with only 3 deaths; time was when we would fix all the fractures. All this has changed, usually for the better, and with it, of necessity, has altered the role of our Journal. As technical specialities have proliferated and prospered so has there been a perceived need to multiply journals. This follows the feeling that the existing pathway of publication is not receptive to a nascent subdiscipline. Such becomes more true if a club, society or some international group is formed. Finally, a new field or a society may feel the need for a standard bearer in the form of its own journal.

All these factors lie behind the steady, and it would seem relentless, proliferation of new journals and the occasional wounded cry of existing ones that they are becoming intellectually and financially emasculated. Though we have no set policy at *The British Journal of Surgery*, it is fairly clear that over the last quarter century we have lost, for the reasons given, a lot of our generality or, to put it another way, we have become a journal of 'general' surgery, when that entity is increasingly what some would describe as the rump but which we believe is the core of the old concept of surgery which followed the post-Listerian explosion. In the last year our major publication themes relating to original work, reviews and leaders has been split between major areas as follows: gastrointestinal, 40 per cent; oncology, 24 per cent; vascular, 15 per cent and breast, 7 per cent. This does not mean there have not been any other articles on such matters as transplantation, paediatrics, plastic surgery, urology and trauma, only that the numbers are small for these areas.

Most of the trend is inevitable but it is a little disappointing not to see more interesting accounts of some of the growing edges of clinical science and practice and to realize that we are offering our readers only one particular window on the total field of surgery. We will of course continue to welcome articles of high scientific or clinical merit in any field and from any source. We would particularly like to stress that we regard it as part of our tradition and of our long-standing relationship with the Association of Surgeons that a significant amount of the work that we publish should originate in places other than recognized and conventional centres of surgical research.

Perhaps we are at the nadir of the relationship between 'generalist' and 'specialist'. We can look, or hope for, a retribalization of subdisciplines so that specialists will still truly care about and understand the core of surgery which includes good diagnostic ability (increasingly supported by computing), an understanding of basic processes in tissue injury, intermediary metabolism and immunology (including both transplantation and host defence against infection and tumour), allied to good technical performance which can be achieved only through meticulous attention to detail and the use of workshops and simulators. We look upon our current role as a response to history. We would like to be *general* for surgery in the way that the *Lancet*, *British Medical Journal* and *New England Journal of Medicine* are *general* for medicine as a whole.

Another aspect of our Journal that has changed and continues to do so is its international flavour. Twenty-five years ago it would have been regarded as rare for a paper to be submitted, let alone accepted, from beyond our shores. Now it is a commonplace and the Table on p. 342 shows how far-flung are our contributors. To a certain extent this is matched by our distribution which goes all over the world and who knows whether at some future date the adjective in our title, already smaller on the

0007–1323/87/050341–02$3.00

Table 1 *Geographical distribution of published papers in the BJS (4 month period)*

UK	50	Oceania	4
North America	5	Middle East	3
Europe	11	Indian Sub-continent	2
Africa	5	S. America	1

front page than it was a decade ago, will not disappear? We live and work in a multinational environment; surgery is an international discipline and we look forward to being *primus inter pares* in this field.

H. A. F. Dudley

Chairman of the Editorial Committee

A. A. Gunn

Editorial Committee Member, 1979–87

Review

Br. J. Surg. 1987, Vol. 74, May,
343–345

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Splenic trauma and overwhelming postsplenectomy infection

This review examines the incidence and implications of overwhelming infection in patients who have undergone splenectomy following trauma.

Few topics have been so widely discussed in the last 10 years as the treatment of splenic trauma. Although splenectomy was considered the treatment of choice until recently, it is now held responsible for the onset of overwhelming postsplenectomy infection (OPSI) immediately or many years after surgery[1].

A large number of experimental and clinical studies from all over the world have contributed to our understanding of the physiology of the spleen and its role in the immunological defence against bacterial infection[2–4]. Several alternatives to splenectomy (non-operative treatment, splenic embolization, ligation of the splenic artery, splenorrhaphy, partial splenectomy, spleen autotransplantation) have been suggested and adopted after careful experimental studies[5–8]. Far from clarifying the ideal treatment for splenic trauma, the great mass of data render the choice of surgical treatment even more confusing. This is mainly due to failure to define the precise incidence of OPSI after splenectomy for trauma. The aim of this review is to stimulate a rational approach to resolve these problems.

Definition of OPSI

Although it is believed that Morris and Bullock were the first to hypothesize an increased incidence of infection after splenectomy in 1919[9], it was not until 1952 that OPSI became seriously considered. In fact in that year King and Shumacker reported that two of five children who underwent splenectomy for spherocytosis died from the sudden onset of OPSI[10].

The clinical picture of OPSI is generally agreed[11–13]. The onset is sudden, the patient presenting with nausea, vomiting and mental confusion. He then goes into a coma and death occurs within a few hours of the onset of symptoms. Disseminated intravascular coagulation, severe hypoglycaemia, electrolyte imbalance and shock are frequently associated with OPSI[14]. In our view, this clinical picture should be present when OPSI is diagnosed. On the contrary many authors have included under the heading OPSI other pathologies, such as subphrenic abscesses and laparotomy wound infections. These are related to the trauma but we do not think that they should be part of the OPSI syndrome as they are not 'specific' septic events linked to splenectomy. In fact, they can also be observed after trauma to the liver, pancreas and especially to the large bowel.

It is not easy to give a precise evaluation of the incidence of OPSI despite the wealth of published information. In our opinion an exact definition of OPSI must be established, especially in the immediate postoperative period as fever, leucocytosis and pulmonary infections frequently occur also after other types of surgery. It is also vital to differentiate between data concerning OPSI incidence and mortality rate in patients splenectomized for splenic trauma and those operated on because of haematological diseases.

Incidence of OPSI

O'Neal and McDonald reported 256 adults who had undergone splenectomy[15]; 187 of them had had splenic trauma, even though patients whose spleen had been removed because of injury incurred in the treatment of other lesions were included in this group. The remaining 69 patients underwent splenectomy for haematological reasons or neoplastic processes in other organs which had spread to the spleen. Four patients in the first group died from OPSI, an incidence of 2·1 per cent.

Livingstone *et al.*[16] studied 236 patients who were splenectomized for trauma, 27 of them being children. The operative mortality was 12 per cent. However, many of these patients were severely shocked when they reached the operating theatre and OPSI was not observed.

In reviewing the literature, Vilde[17] collected 688 cases of splenectomy following splenic trauma and noted 4 deaths caused by OPSI (0·6 per cent).

In their series of 641 patients who underwent splenectomy for trauma, Sekikawa and Shatney[18] reported systemic sepsis in 114 of them. This seems to confirm the increased incidence of OPSI in splenectomized patients. However, they reported that none of the 15 children had suffered from these septic episodes, while it is known that they have the highest incidence of the syndrome. They also reported that the increase of septic complications paralleled the severity of the trauma and the number of organs involved. This demonstrates the non-specificity of the clinical picture. Long-term follow-up was carried out in 242 patients, 6 of whom presented severe septic episodes, but none died. These authors conclude that the many factors that can be responsible for infections in traumatized patients hinder the evaluation of the effects of splenic removal.

Another interesting series of 200 adults with splenic trauma was reported by Moore *et al.*[19]. They compared patients who underwent splenectomy with those who received alternative treatment. In the 85 patients who underwent splenorrhaphy, 2 died from sepsis-related multiple organ failure. In this group of patients there were complications such as pneumonia and major atelectasis, complications which are usually attributed to asplenia when observed in splenectomized patients. A subphrenic abscess was seen in one patient in whom jejunal resection had been necessary.

Malangoni *et al.*[20] examined 245 patients who underwent splenectomy following trauma; 68 of them developed postoperative infections (pulmonary, urinary tract, intra-abdominal, wound). It is likely that these were also non-specific infective complications as the incidence of infections increased progressively with the number of associated lesions. For

0007–1323/87/050343–03$3.00

example, it rose from 7 per cent in patients with isolated splenic trauma, to 64 per cent in those with four or more associated lesions. In the 68 patients with infective complications, 21 developed sepsis, the incidence varying from 2 per cent in patients with isolated splenic trauma to 32 per cent in those with four or more associated lesions. Thirteen of the twenty-one patients with sepsis died, but since the incidence of associated lesions was very high, OPSI cannot be held responsible as the cause of death. These authors carried out a long-term follow-up on 140 patients and reported only three episodes of sepsis, none of which was fatal.

Pate *et al.*[21] reported a study of 420 splenectomized patients. Splenectomy was performed for trauma in 158 cases, as an incidental procedure in 91, for haematological reasons in 67 and before renal transplantation in 104 patients. Excluding the last group of 104 cases, the immediate mortality rate was 8 per cent. Even though the causes are not specified, death could be attributed to shock. Late onset of OPSI was responsible for death only in one 6-year-old child who was splenectomized for haematological disease. None of the 13 other patients who died at some time after surgery developed OPSI.

In the 228 adults splenectomized for splenic trauma and reported by Vichard and Dreyfus-Schmidt[22], there were 4 cases of fatal OPSI (2·2 per cent). No cases of OPSI were observed by Chaikof and McCabe[23] in their series of 77 patients who were splenectomized as a result of splenic trauma.

The total number of patients reported in the literature as dying from OPSI is 12 (4 reported by O'Neal and McDonald; 4 by Vilde; 4 by Vichard and Dreyfus-Schmidt) out of 1816 patients undergoing splenectomy, an incidence of 0·66 per cent.

Our own series comprised 148 splenectomized patients (72 splenectomized for haematological reasons, 69 for trauma, 2 for incidental reasons and 5 others for miscellaneous causes) revealed no cases of fatal OPSI. In the patients who were splenectomized for haematological reasons, 19·4 per cent had episodes of high fever lasting less than 48 h. These disappeared after medical therapy. No serious instances of sepsis were observed. In the patients who were splenectomized for trauma no cases of OPSI were observed, although some of them developed less severe sepsis which was attributed to associated lesions.

Implications of OPSI for the management of splenic trauma

determination that splenectomy in adults necessarily leads to a measurable increased risk of developing overwhelming late sepsis'. His words were taken up by Sherman, who called for the introduction of a special splenic trauma registry to make up for the lack of precise data regarding OPSI incidence.

It was our own feeling that the high number of conservative operations performed after splenic trauma was a step ahead of the surgical techniques (especially partial organ resection with previous ligation of the splenic artery branches), but we were not certain that the very low incidence of OPSI after trauma justified them. In fact, we have not observed any cases of immediate postoperative OPSI in the 148 patients who have been splenectomized in our department. At present we are carrying out an evaluation of the incidence of late sepsis and long-term alteration of the immunological system induced by splenectomy.

For the purpose of the present review we have evaluated the results obtained from series published from 1981 to today using restrictive criteria, i.e. we classified as OPSI only the cases which adhered to the classic description of OPSI and excluded postoperative cases of sepsis after trauma which could not be attributed to the splenectomy. Examination of the data obtained from the 1816 patients reviewed revealed fatal OPSI in 12 cases, an incidence of 0·66 per cent. It must be borne in mind that whereas O'Neal and McDonald included some so-called 'incidental' splenectomies as post-traumatic, one cannot exclude factors linked to the primary operation in such patients[15]. Furthermore the 4 cases of OPSI observed by Vichard and Dreyfus-Schmidt in 228 patients who were splenectomized for trauma require careful evaluation[22]. In fact, they reported that the OPSI occurred in polytraumatized patients and its aetiology stemmed from Gram-negative bacteria (2 *Proteus*, 1 *Escherichia coli*) in three cases and from streptococcal infection in the remaining case. No cases were caused by pneumococcal infection, the organism responsible for 50 per cent of OPSI cases.

Therefore, by excluding these two series the number of cases of OPSI falls to four, an overall incidence of 0·28 per cent. If we take into account the 69 patients splenectomized for trauma in our own unpublished series, none of whom developed OPSI, the mortality rate from OPSI falls to 0·27 per cent.

However, the problem is far from being solved. Apart from the doubts concerning OPSI as the unequivocal cause of death, who can be certain that this mortality rate is so low that

[redacted]

alongside ones without recognizable splenic parenchyma. In our opinion these discordant results cannot be foreseen and may be attributed to local anatomical vascularization factors.

Velcek[48] is correct in stating that the question regarding the reduction or elimination of OPSI by spleen autotransplantation can only be answered after a careful statistical analysis of a large number of patients who have undergone this type of surgery. Furthermore, splenic autotransplantation could slow down the course of OPSI and allow diagnosis and immediate treatment. The correct definition of the role played by spleen autotransplantation may help to resolve the therapeutic problems encountered in splenic trauma.

Further retrospective and prospective studies on large groups of patients must be carried out before an 'ideal' operation can be suggested for splenic trauma. Perhaps there will never be an ideal treatment, but, as in other pathological conditions, this may vary from case to case.

Acknowledgements

We would like to thank Mrs Moira Macpherson for help in translating the paper.

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Br. J. Surg. 1987, Vol. 74, May,
346–349

Splenectomy for massive splenomegaly

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Splenectomy was performed on 47 patients with massive splenomegaly (spleen weight $>1{\cdot}5$ kg). With one exception, all patients had a haematological malignancy. The indications for splenectomy were for the diagnosis of unknown cause (n=5), for the relief of pain (n=8), as the initial treatment of hairy cell or prolymphocytic leukaemia (n=8), and for the correction of a haematological cytopenia (n=26). Splenectomy was completely successful in relieving pain and in establishing a diagnosis, and provided effective palliation in patients with hairy cell and prolymphocytic leukaemia. An immediate correction of a haematological cytopenia was achieved in 24 patients, and the correction was maintained for over 1 year in 11 patients. There were no postoperative deaths and morbidity was acceptably low. We conclude that patients with massive splenomegaly can derive considerable benefit from splenectomy and that massive splenomegaly should not be regarded as a contra-indication to splenectomy.

Keywords: Splenectomy, splenomegaly, lymphoma, leukaemia, lymphocytic

Splenectomy is commonly performed for the diagnosis and treatment of lymphomas and haematological disorders. Numerous reports have testified to the value of the procedure[1–3] but these reports have described mainly the removal of normal sized, or only moderately enlarged spleens. Although there is little information on splenectomy for massive splenomegaly, the operation is commonly believed to be hazardous and to provide only poor palliation. In 1978, Goldstone reported that beneficial results could be achieved by splenectomy for massive splenomegaly, but only at the cost of a high operative mortality[4]. Wobbes *et al.*[5] later reported that massively enlarged spleens could be removed with a low mortality, but they made no comment on the efficacy of the procedure in terms of palliation or correction of any associated haematological abnormality. As one of us (P.J.M.) has been responsible for the haematological surgery in Oxford for the past 11 years, we have taken the opportunity to review our experience of splenectomy for massive splenomegaly in 47 patients. The results show that these patients benefited considerably from splenectomy, and that this was achieved with no mortality and an acceptable morbidity.

Patients and methods

Between 1975 and 1985, 311 patients had an elective splenectomy under the care of one of us (P.J.M.) as part of the treatment of neoplastic or haematological disease, as part of a staging laparotomy or as part of the investigation of splenomegaly of unknown cause. Prospective personal records are maintained for all patients referred for splenectomy. Massive splenomegaly, defined by Goldstone as a spleen weighing 1·5 kg or more[4], was present in 47 of these patients.

More than half of the patients with massive splenomegaly were 60 years of age or older (*Figure 1*), and there were 32 males and 15 females. With one exception, all the patients had a malignant disease, and the final pathological diagnoses are shown in *Table 1*. Thirty patients had received cytotoxic therapy and eight patients had received splenic irradiation before splenectomy. Significant cardiac or respiratory disease was present in 23 patients.

Splenectomy was performed in 26 patients with hypersplenism in an attempt to correct a haematological cytopenia. In six of those patients, the cytopenia did not allow the patient to tolerate appropriate chemotherapy at the full dosage. Other reasons for splenectomy were for the relief of abdominal pain or discomfort in eight patients, as the initial treatment of the disease in eight patients with hairy cell or prolymphocytic leukaemias, and for the diagnosis of splenomegaly of unknown cause in five patients (*Table 2*).

Thirty-four patients (72 per cent) had a haematological cytopenia, although this was not the primary indication for splenectomy in all these cases. Seven patients had anaemia alone (haemoglobin <10 g/dl), and ten patients had thrombocytopenia alone (platelet count $<100\times10^{-9}$/l). Ten patients had thrombocytopenia and anaemia, three patients had anaemia and leukopenia (white cell count

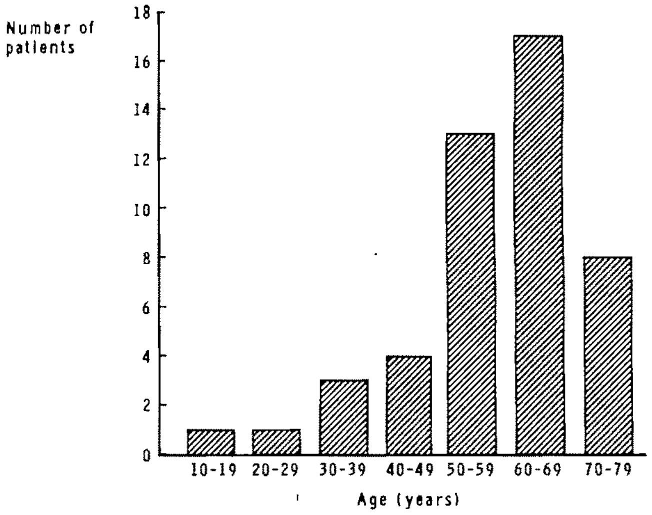

Figure 1 *The age distribution of patients with massive splenomegaly undergoing splenectomy*

Table 1 *Pathological diagnosis in 47 patients with massive splenomegaly*

Diagnosis	No.
Non-Hodgkin's lymphoma	19
Chronic lymphatic leukaemia	12
Hairy cell leukaemia	5
Prolymphocytic leukaemia	3
Hodgkin's lymphoma	3
Myelofibrosis	2
Chronic myeloid leukaemia	2
Sarcoidosis	1
Total	47

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Table 2 *The indications for splenectomy*

	No.
Correction of a haematological cytopenia	26
Relief of abdominal pain	8
Primary treatment*	8
Diagnosis	5
Total	47

* Hairy cell leukaemia or prolymphocytic leukaemia

$<3\times10^{-9}$/l), one patient had leukopenia and thrombocytopenia, and three patients had pancytopenia. Overt bleeding was present in five patients, and bruising or petechiae were present in an additional seven patients, all with thrombocytopenia.

All patients were admitted for an elective splenectomy, but one patient developed a strangulating inguinal hernia which required an emergency operation and splenectomy was performed at the same time. A generous midline or muscle splitting paramedian incision was used for the majority of patients, but a subcostal incision was found to be satisfactory if the costal margin was wide and if the spleen did not extend to the umbilicus. In no case was a thoraco-abdominal incision required for access. The difficulty of the operation was determined largely by the presence or absence of adhesions between the spleen and diaphragm and parietal peritoneum. In the absence of adhesions a conventional splenectomy was performed and the stretched ligaments usually allowed the spleen to be mobilized out of the wound without difficulty. Extensive vascular adhesions were encountered in approximately half of the patients. These adhesions were divided under direct vision and the bleeding controlled systematically by ligation or diathermy. When the adhesions were particularly extensive the gastrosplenic ligament was divided and the splenic artery ligated before beginning division of the adhesions. After the division of vascular adhesions the splenic bed was always drained but plication of the floppy diaphragm was not performed. Platelet concentrate was infused after the ligation of the splenic vessels in nine patients with severe thrombocytopenia (platelet count $<50\times10^{-9}$/l). Lymph node, bone and liver biopsies were usually performed. Two patients had a cholecystectomy and one patient referred to above had a small bowel resection and inguinal herniorraphy performed in addition to the splenectomy. One patient with a non-Hodgkin's lymphoma required a distal pancreatectomy as extensive lymph node involvement at the splenic hilum did not allow access to the splenic vessels beyond the tail of the pancreas. The weights of the spleens are shown in *Figure 2*.

During the period of the review, 264 patients with spleens weighing less than 1·5 kg underwent an elective splenectomy. The mean age of this group was 36 years (range 6–78) and included 146 patients with Hodgkin's disease who had a splenectomy performed as part of a staging laparotomy.

Results

All patients who underwent splenectomy for massive splenomegaly were discharged from hospital and there were no deaths within 30 days of operation.

The operation was successful in all eight patients in whom the splenectomy was performed primarily for the relief of abdominal pain. One patient is alive 2 years after the operation, while the other patients died between 9 months and 5·5 years after the operation (median survival time of 17 months). Relief of abdominal pain or discomfort also followed splenectomy in nine other patients in whom this was not the primary indication for surgery. Thus significant palliation was obtained in this group of patients.

Splenectomy provided an unequivocal histological diagnosis in all five patients with splenomegaly of unknown cause. Two patients had Hodgkin's lymphoma (one died 6 years after operation, the second is alive 14 months after operation), and two patients had non-Hodgkin's lymphoma (both alive at 1 and 5 years). The fifth patient was found unexpectedly to have sarcoidosis and he is alive 7 months after the operation.

Two patients with hairy cell leukaemia died at 1 and 7 years after operation, and three patients are alive having survived 1, 6 and 8 years. One patient with prolymphocytic leukaemia died 1 year after operation, the other two patients have so far survived for 1 year.

An immediate haematological correction was achieved in 24 of the 26 patients who underwent splenectomy primarily for the reversal of a cytopenia. The two patients who failed to respond died at 2 and 6 months after the operation. Two patients were lost to follow-up. The cytopenia recurred in 11 patients, all of whom died between 4 and 31 months after splenectomy. Four patients remained haematologically normal until they died of other complications of their disease at 6, 10, 17 and 56 months after operation. The remaining seven patients are alive with a normal haematological picture between 1 and 6 years after operation. Only 6 of the 13 patients who failed to respond to splenectomy, or relapsed after splenectomy are alive 1·2 months after the operation. Nine of the eleven patients who remained haematologically stable after splenectomy survived 12 months, and five of these patients have survived for longer than 2 years. Of the six patients who were operated upon because of intolerance to cytotoxic therapy, four were able to resume treatment at full dosage, and in two patients chemotherapy was found to be no longer necessary.

A postoperative complication occurred in 24 of the 47 patients (51 per cent) (*Table 3*). The commonest complication was a chest infection, but in the majority of cases the infection was mild and responded rapidly to treatment. One patient developed a pleural effusion which required drainage. One patient had a significant haemorrhage after splenectomy but this was managed successfully by blood transfusion. One patient developed acute cholecystitis which required cholecystectomy in the postoperative period. The mean duration of postoperative

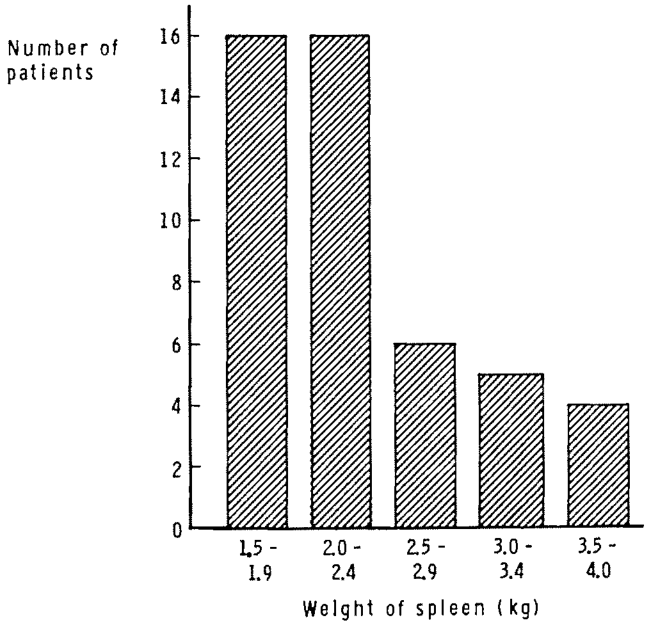

Figure 2 *The weight distribution of the spleens removed at operation*

Table 3 *The complications of splenectomy*

	No.	Percentage
Chest infection	16	34·0
Wound infection	6	12·8
Deep venous thrombosis	3	6·4
Pulmonary embolism	1	2·1
Pelvic abscess	1	2·1
Haemorrhage	1	2·1
Paralytic ileus	1	2·1
Acute cholecystitis	1	2·1

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recovery (from operation to discharge from hospital) was 10·9 days (range 6–36 days). Thirty patients (64 per cent) were discharged on or before the tenth postoperative day, and only seven patients (15 per cent) remained in hospital for longer than 2 weeks after the operation. A reactive thrombocytosis (platelet count $>700 \times 10^{-9}$/l) occurred in 17 patients (36 per cent), of whom six had been thrombocytopenic before the splenectomy. In all cases the thrombocytosis resolved within 3 weeks, and a deep venous thrombosis occurred in only one patient. There was no correlation between the incidence of complications and the size of the spleen, the nature of the underlying disease or the patients' haematological status.

Of the 264 patients with spleens weighing $<1·5$ kg who underwent an elective splenectomy, all were discharged from hospital and no patient died within 30 days of operation. A postoperative complication occurred in 50 (18·9 per cent) of these patients (this will be the subject of a separate report).

Discussion

In Europe and North America massive splenomegaly is usually the result of haematological malignancy. Such patients are usually incurable, and so the potential benefits of diagnostic or palliative splenectomy must be carefully balanced against the possible risks. A precise assessment of the risks, and more particularly of the benefits of the procedure, is not possible because of the uncontrolled nature of our review, but we believe that for the majority of our patients the operation was worthwhile.

We consider the five diagnostic splenectomies to have been worthwhile as they provided a firm diagnosis upon which later treatment was based. The four patients with a lymphoma all achieved a remission after the appropriate chemotherapy, and the fifth patient, who was found unexpectedly to have a benign disease, was spared unnecessary and harmful cytotoxic therapy. Splenectomy performed for the relief of pain produced gratifying results as not only were all the patients relieved of their distressing symptom but, with the exception of two patients, they all survived free of pain for at least 12 months. Prolymphocytic and hairy cell leukaemia are diseases which are known to respond poorly to chemotherapy, but which can often be controlled successfully by splenectomy[6]. Our results support the opinion that splenectomy can be beneficial in this disease even in the face of massive splenic involvement[7].

The value of splenectomy for the correction of haematological cytopenias in lymphoproliferative disease was controversial in the past as early reports were discouraging[8,9]. However, good results have been reported from more recent studies[10–12].

All of our patients who had severe cytopenias had proved unresponsive to conventional treatment either with chemotherapy or splenic irradiation. Although the prognosis for such patients is extremely poor, a haematological correction was achieved in 24 of the 26 patients, and many of the responders survived for appreciable periods. Our results are broadly similar to those previously reported by one of us (P.J.M.)[10,13] from a series of patients with spleens of various sizes, and indicate that massive splenomegaly does not preclude a satisfactory response to splenectomy.

The absence of perioperative mortality in our series of patients with massive splenomegaly compares favourably with the mortality rate of 14·7 per cent reported by Goldstone[4], and the 6·4 per cent reported by Sharpe *et al.*[14]; and is similar to the 2 per cent reported by Wobbes *et al.*[5] The high incidence of postoperative complication following splenectomy for massive splenomegaly is similar to that reported in these series. Most of the complications were relatively mild and only a few patients had a protracted convalescence. In contrast to previous reports, postoperative haemorrhage occurred in only one of our patients. Although we were careful to achieve satisfactory haemostasis we did not routinely use either preliminary ligation of the splenic artery or injection of adrenaline into the splenic artery. Preliminary ligation of the splenic artery has been shown to reduce intra-operative bleeding[4] and can be a helpful manoeuvre, but we do not recommend the use of adrenaline, as shock following the procedure has been reported[15]. Platelet transfusions were given to patients with severe thrombocytopenia immediately after ligation of the splenic vessels, and no haemorrhage occurred in these patients. The provision of appropriate haematological support is obviously essential in the preparation and postoperative management of these patients.

The incidence of complications in patients with massive splenomegaly was approximately double that found in the patients who had an elective splenectomy for spleens $<1·5$ kg in size. However, the composition of the two groups differed with the patients with smaller spleens being generally healthier and younger than those with massive splenomegaly. We agree with the opinion of Wobbes *et al.*[5] that the higher morbidity following splenectomy for massive splenomegaly is a function of the underlying disease and general condition of the patient rather than of the size of the spleen.

These results confirm that splenectomy for massive splenomegaly can result in substantial benefits for the patient in terms of palliation for pain and correction of haematological abnormalities, and can be achieved with an acceptable incidence of morbidity. We do not, of course, advocate that splenectomy should be delayed until the spleen has become greatly enlarged, but suggest that massive splenomegaly should not be regarded as a contra-indication to splenectomy. We have, in fact, felt it appropriate to offer splenectomy to all patients referred for consideration for splenectomy, and just as we have stated previously concerning splenectomy for hypersplenism in patients with haematological malignancies[10,13] the presence of widespread disease does not preclude splenectomy, as the benefits may be substantial. However, the management of these patients by an experienced group is probably of significance in achieving the results reported in this analysis.

Acknowledgement

We thank the members of the Oxford Regional Lymphoma Group, the Department of Haematology, and the Nuffield Department of Medicine for their referrals, and gratefully acknowledge their assistance in the management of these patients.

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Paper accepted 25 January 1987

Case report

Br. J. Surg. 1987, Vol. 74, May, 347

Intraperitoneal haemorrhage into an undiagnosed patent processus vaginalis simulating an incarcerated hernia

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Neglected incarcerated inguinal herniae carry a considerable morbidity and mortality, and it is common surgical practice to explore all cases in which the diagnosis is suspected. Inevitably, this policy leads to unexpected findings. This report adds a hitherto unpublished differential diagnosis.

Case report

An 85-year-old man was admitted for a bleeding duodenal ulcer. Due to recurrent bleeding a laparotomy with transfixion of the ulcer and a truncal vagotomy with a pyloroplasty was performed. Recovery was uneventful until the seventh postoperative day, when a deep venous thrombosis of the left calf was diagnosed. Anticoagulation with warfarin was started. The prothrombin index was in the therapeutic level within 3 days, and it remained within that range.

On admission no signs of hernia or hydrocele were noted. On the eighth day a 5 × 4 × 3 cm, soft, non-tender tumour was discovered in the right groin. There was no abdominal tenderness, and bowel sounds were normal. Within the next 2 days the tumour became tense and tender, and a strangulated inguinal hernia was suspected. Under general anaesthesia the right groin was explored through a transverse incision. In the subcutaneous tissue, just distal to the external inguinal ring, a 6 × 5 × 4 cm dark, tense, cystic tumour was found, partly covered by cremaster fibres. The external aponeurosis was opened. The cord was dissected, and a persisting vaginal process communicating with the cyst was demonstrated. Distally to the cyst, the vaginal process was obliterated (*Figure 1*). The cyst and the patent vaginal process were removed. Through the internal inguinal ring blood was seen in the peritoneal cavity, and 200 ml sucked out. The neck of the sac was transfixed, and the external aponeurosis and the wound were closed. The recovery was uneventful.

After the operation the sac was opened. The process was empty, while the cyst was filled with blood. Separating the two, at the level of the external inguinal ring, was a valve-like arrangement.

Discussion

This patient probably had a patent processus vaginalis of a small calibre communicating with a hydrocele in the cord, a condition designated intermittent funicular hydrocele by McVay[1]. Under normal conditions the patent processus has allowed the peritoneal fluid, but not abdominal organs, to enter freely in and out of the hydrocele. When a haemoperitoneum developed after the operation, the formation of a clot hindered the free passage of blood, and the cyst became symptomatic.

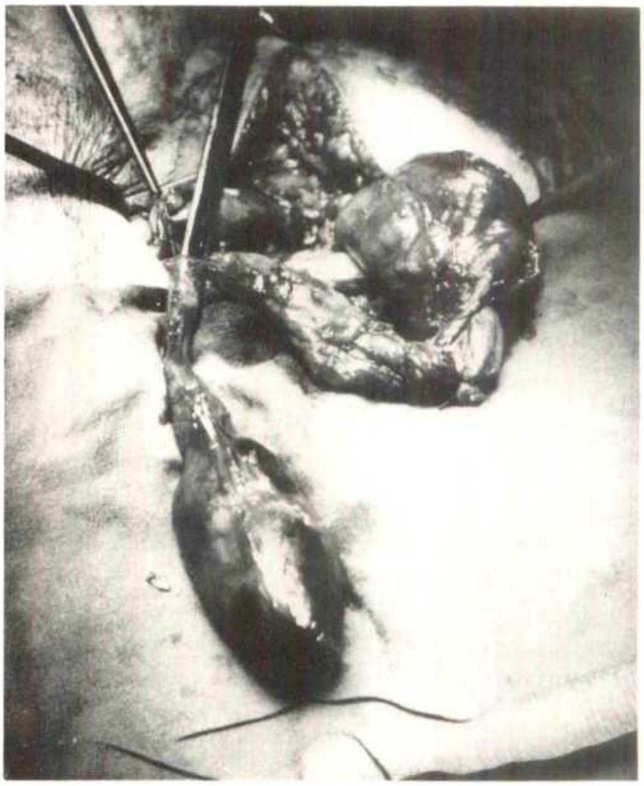

Figure 1 *The cyst and the persisting vaginal process have been dissected from the other contents of the cord. The patent process is probed with scissors*

Strangulated or incarcerated inguinal herniae may be simulated by a variety of developmental, inflammatory, neoplastic and degenerative conditions, inside as well as outside the inguinal canal[2]. When ascites, dialysis fluid[3] or blood[4] leaks into a recognized inguinal hernia sac the diagnosis may be made without exploration. However, in cases in which the patent processus is unrecognized the diagnosis can only be suspected.

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Paper accepted 6 October 1986

0007-1323/87/050349-01$3.00

Br. J. Surg. 1987, Vol. 74, May,
350–352

Spleen-saving procedures in paediatric splenic trauma

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The aim of this study is to assess the advantages of 'spleen-saving procedures' in paediatric splenic trauma. Since January 1979, 87 children with splenic trauma were treated. Six were treated without operation. Eighty-one patients were treated surgically. Sixteen cases with type I splenic injury were subject to simple splenorrhaphy, and twenty-three cases with type II splenic injury underwent splenorrhaphy plus omentoplasty. Twenty-four cases had type III splenic injury; of these, 20 were treated by ligation of the splenic artery (the main splenic artery in 14 cases and the upper segmental artery in six cases) with splenorrhaphy and omentoplasty, and the remaining four cases were treated by partial splenectomy and omentoplasty. In 16 of the 18 patients with type IV splenic injury, splenectomy was inevitable and heterotopic splenic autotransplantation was added. In the remaining two cases, it was possible partially to preserve the spleen. No complication was observed due to any of these spleen-saving procedures. Moreover, splenic implants increased complement C_3 levels and improved filtration function. Despite other injuries, the mortality rate of this group was 5·7 per cent. The splenic salvage rate was 82 per cent.

Keywords: Postsplenectomy sepsis, splenic salvage, splenic autotransplantation

The indications for conservation of splenic tissue in children have been reinforced by a growing knowledge of the physiological and immunological functions of the spleen. Splenectomy in childhood increases the risk of death due to serious infections. Patients splenectomized for trauma have a similar risk to those splenectomized for haematological diseases but to a lesser degree and young children seem to fare worse than older children and adults. The syndrome of 'overwhelming postsplenectomy infection' (OPSI) has a sudden onset and high mortality rate[1,2]. The incidence of fulminating sepsis in asplenic children following trauma is 85 times that in the normal population[3].

At present, many different spleen-saving procedures are in use. In this study, we present our experience with some of these techniques.

Patients and methods

These data have been collected by retrospective review of patients with splenic injuries treated between January 1979 and May 1986. Eighty-seven children with splenic injuries due to blunt abdominal trauma were treated. There were 63 males and 24 females. The median age was 6·5 (range 1–14 years). Motor vehicle accidents were the major cause.

Besides routine clinical and laboratory investigations, ultrasonographic, radiological and scintigraphic examinations were evaluated for the diagnosis of splenic injuries. Macroscopic and microscopic examination of the peritoneal fluid was always performed.

Patients with the following criteria were selected for non-operative treatment: (a) haemodynamically stable with transfusion requirements lower than $40\,\mathrm{ml\,kg^{-1}}$ $24\,\mathrm{h^{-1}}$; (b) superficial and limited splenic injuries as assessed by scintigraphic and ultrasonographic examinations; (c) the absence of other intra-abdominal injury.

In cases that were subjected to laparotomy, splenic injuries were staged according to the classification of Upadhyaya and Simpson[4] (*Table 1*). In type I–III injuries the spleen was preserved totally or partially. In type IV injuries splenectomy plus heterotopic splenic autotransplantation was the treatment of choice. For splenic autotransplantation two to four 3 cm × 5 cm × 0·5 cm decapsulated splenic slices were placed in two omental rows and kept in place with 3/0 catgut sutures. Unless there was an intra-abdominal accessory injury, no abdominal drain was needed.

Follow-up was by clinical examinations at 3 month intervals. In children with totally or partially preserved spleens, scintigraphic examinations were done at the end of the first week and third month. In the postoperative evaluation of the autotransplanted group, additional tests were performed: (a) splenic scintigrams were taken at the third month, first and fifth year postoperatively; (b) Howell–Jolly inclusion bodies were assessed at the third month and fifth year postoperatively—for each case, at least 3000 red blood cells were examined in each peripheral blood smear; (c) immunological parameters: immunoglobulin (IgG, IgM, IgA) and complement C_3 and C_4 levels were measured by 'single radial immunodiffusion method'[5,6]. T and B lymphocytes were counted by Brain's 'rosette formation method' and Papamichael's 'immunoglobulin on the surface human lymphocyte' test[7,8]. Miller's phagocytosis method was used for the measurement of opsonic activity[9]. All of these investigations were done in the early and late postoperative periods.

A group of 10 children who were splenectomized previously for blunt abdominal trauma were taken as a control group. The median age of this group was 9·5 (range 3–14 years); six of them were male and four were female. Scintigraphic examinations as well as the same laboratory investigations mentioned above, were performed in this control group. All results are expressed as mean ± standard error of the mean. Statistical differences were assessed using the 'Student's *t* test'.

Results

In 6 of the 87 cases, non-operative treatment was tried initially and no surgical treatment was subsequently needed in these patients. The mean follow-up period was 6·3 months (range 2 months to 1·5 years). During that time no complications were observed.

Table 1 *Types of splenic injuries*

Type I	Incomplete parenchymal tear
Type II	Parenchymal tear extending up to the hilus, but not dividing it
Type III	Complete parenchymal tear dividing the spleen into two fragments, each with an intact blood supply
Type IV	Complete fragmentation with a torn hilar vessel. The extravasated blood has filled the peritoneal folds of the hilus

The procedures used in the 81 patients who were treated surgically are presented in *Table 2*. In type I and II injuries surgery was straightforward. In 4 of the 24 cases with type III injuries partial destruction of splenic parenchyma was seen; in these cases, segmental artery ligation with partial splenectomy and omentoplasty was performed. In two of the 18 patients with type IV injuries, the short gastric vessels seemed to be intact allowing preservation of some splenic tissue. In the other 16 cases splenectomy was inevitable.

Table 2 *Spleen-saving surgical procedures according to the type of splenic injuries*

Type of splenic injury	No. of cases	Surgical treatment
Type I	16	Simple splenorrhaphy
Type II	23	Splenorrhaphy + omentoplasty
Type III	24	
	20	Splenic artery ligation + omentoplasty + splenorrhaphy (ligation of the main splenic artery in 14 cases and ligation of the upper segmental artery in 6 cases)
	4	(with partially destroyed parenchyma): Partial splenectomy + omentoplasty
Type IV	18	
	16	Splenectomy + heterotopic splenic autotransplantation
	2	Partial splenectomy + omentoplasty
Total	81	

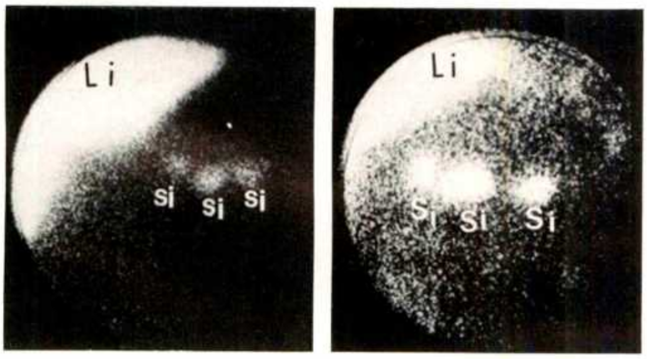

Figure 1 *Left: scintiphotogram of the three splenic implants (third postoperative month). Right: scintiphotogram of the late postoperative period (fifth year). Li, liver; Si, splenic implant*

In 71 of the 87 patients in whom the spleens were preserved partially or totally, early and late scintigrams revealed intact and functional splenic tissues. In 8 of 71 cases, areas of low uptake were seen in the initial scintigrams; later scintigrams were however normal.

In the splenic autotransplantation group, 16 children were followed for 5 years. In their scintigraphic examinations, all splenic implants appeared in the midabdomen, just below the liver (*Figure 1*). It was also observed that the dimensions and intensity of splenic images had increased in all cases by the end of the fifth postoperative year. The results of laboratory investigations are presented in *Table 3*. According to these findings, splenic implants were significantly different from splenectomized controls only in their complement C_3 levels ($0{\cdot}02 > P > 0{\cdot}01$). The implants appeared to have an effective filtration function. The mean number of Howell–Jolly bodies was significantly lower in the autotransplantation group than in the control group ($P < 0{\cdot}001$).

During the follow-up period, no OPSI was seen. There was one life-threatening pulmonary infection in the control group, which was successfully treated.

For all cases the median stay in hospital was 8·2 days. In the non-operative group (six cases), a resting period at home (3 weeks) was advised. No secondary surgical intervention for intra-abdominal bleeding was required and no complication due to heterotopic splenic autotransplantation was seen. In the early postoperative period, 10 patients had minor complications (wound infection in 4, atelectasis of the left lower lobe in 4, urinary infection in 2). In the late postoperative period, intestinal obstruction occurred in two cases. One of them was treated by division of adhesions. The other resolved without operation. Five of the eighty-seven cases died (5·7 per cent). Serious cerebral injuries were the main cause of death in these patients. Two of them had serious bilateral thoracic injury and one had multiple intra-abdominal injuries.

Discussion

The major changes in the immune system following splenectomy includes: (a) decrease in the number and functions of T and B lymphocytes; (b) stable low serum IgM levels and temporary alterations in IgG and IgA; (c) failure of filtration function and clearance of pitted cells and Howell–Jolly inclusion bodies; (d) decrease in properdin levels and opsonic activity; (e) decrease in complement levels (especially C_3); (f) deficiency in phagocytosis promoting tetrapeptide 'tuftsin'[2,10–12]. For this reason, the philosophy of surgical management of splenic injuries has changed over the past decade. Special suturing and splenic resection techniques (cryogenic surgery, heat coagulation, ultrasonic splenectomy, microwave techniques, infrared radiation etc.) and special tissue adhesives have been developed[10,13–17].

In most cases conventional surgical techniques allowed splenic preservation and we encountered no complication related to surgical technique. The splenic salvage rate for our

Table 3 *The results of laboratory investigations*

	Autotransplantation group (16 patients)	Control group (10 patients; splenectomy)	P value
Mean T cell count	2559·3 ± 1651·6	2097·6 ± 593	$P > 0{\cdot}30$
Mean B cell count	625·8 ± 434·8	421·9 ± 167·3	$P > 0{\cdot}50$
Mean IgA level (mg/100 ml)	128 ± 85·7	189 ± 55·6	$P > 0{\cdot}20$
Mean IgM level (mg/100 ml)	184·5 ± 154·5	177·6 ± 108·8	$P > 0{\cdot}50$
Mean IgG level (mg/100 ml)	2715 ± 1507	2408·6 ± 1156·9	$P > 0{\cdot}10$
Complement-C_3 (mg/100 ml)	114·7 ± 38·5	74·2 ± 14·9	$P < 0{\cdot}01$*
Complement-C_4 (mg/100 ml)	68 ± 20·5	53 ± 21	$P > 0{\cdot}10$
Opsonic activity	4·2 ± 0·3	4·1 ± 0·4	$P > 0{\cdot}30$
Mean Howell–Jolly body count	0·017%	0·19%	$P < 0{\cdot}001$*

* Statistically significant

institution is 82 per cent. This rate has been reported by others at between 70 and 95 per cent[3,18-21]. Most authors believe that in major injuries ligation of the splenic artery leaving the spleen *in situ* has occasionally been successful, but more experience is necessary to assess the efficacy of this approach. In 20 patients with type III splenic injury we have seen no complication or side effect due to splenic artery ligation (the ligation of the main splenic artery in 14 cases and the ligation of upper segmental splenic artery in 6 cases).

During the last 5 years an increasing number of investigators have used non-operative treatment initially[18,20,21]. The high rate of life-threatening other injuries prevented us from choosing non-operative treatment in most of our cases.

When it has been necessary to remove the spleen for traumatic rupture, three methods are available to attempt to lower the incidence of OPSI: (a) prophylactic antibiotic therapy, (b) vaccination and (c) splenic autotransplantation. Antibiotic prophylaxis is effective against half of the organisms associated with OPSI[3,18] but vaccines unfortunately do not cover all possible infecting organisms. For this reason, splenic autotransplantation must be added to these components as a supplementary procedure. Some authors had shown the failure of splenic implants against OPSI[22-25]. But other investigators and we have shown positive immunological and filtration effects of splenic implants[13,19,25,26,27]. For this reason, if no splenic tissue can be salvaged *in situ* by one of the conservative procedures, an attempt should be made to transplant splenic slices into the greater omentum. Spleen-saving procedures are safe and non-time-consuming operations. They can be attempted in cases with multiple injuries.

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Paper accepted 12 December 1986

Br. J. Surg. 1987, Vol. 74, May, 353–357

Splenectomy in the management of haematological disease

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Patients, both adults and children, with various haematological disorders who had splenectomy electively in the diagnosis, staging or treatment of their condition during a 15-year period in the Aberdeen hospitals were reviewed. The outcome regarding the disease and the immediate and long-term complications of splenectomy in this group of 185 patients are presented. Splenectomy has an acceptably low morbidity, even in patients with serious haematological disease, in the hands of an experienced surgical team, where there is close co-operation between surgeon and haematologist. Occasionally, late overwhelming infections may occur, despite prophylaxis with penicillin and pneumococcal vaccination. It seems likely that, in their zeal to report such hazards, authors may allow the pendulum against splenectomy to swing too far, in the direction of leaving patients, especially adults, with considerable symptoms and poor health, rather than risk the occasional consequences of the asplenic state.

Keywords: Elective splenectomy, overwhelming infections, haematological disorders

In recent years, there has been a considerable swing away from performing splenectomy for haematological disease, because of the potential dangers of overwhelming postsplenectomy infection (OPSI). By 1962, it was recognized that the risk was greatest in young children[1–3], in whom infection by capsulated organisms, such as *Streptococcus pneumoniae* and *Meningococcus*, may be rapidly fatal[4,5]. There seems little doubt that splenectomy for auto-immune thrombocytopenia in childhood was at one time performed too lightly, since the risk of life-threatening bleeding, for example cerebral haemorrhage, has been estimated to be very small indeed[6]. Also the vogue for performing splenectomy in all fit patients with chronic granulocytic leukaemia has now passed[7,8]; and the place of staging laparotomy/splenectomy in Hodgkin's disease is being much more carefully defined[9,10].

There remains, however, a definite place for splenectomy in the management of many diseases which either primarily affect haemopoietic tissue, or produce secondary haematological disturbance. Setting out the experience of splenectomy over a prolonged period in one geographical region may allow a balanced view of its place in the management of these conditions to be reached.

Patients and methods

One hundred and eighty-five patients, both adults and children, with various haematological disorders, who had had elective splenectomy in the diagnosis, staging or treatment of their condition in the 15 year period between 1969 and 1983, were reviewed. All had been managed by one or other (usually both) of the two senior authors (P.F.J. and A.A.D.) and long-term follow-up was performed by A.A.D. Patient review has been documented to December 1985.

Patients were referred from the Grampian area of Scotland, Orkney and Shetland. Several patients from the Highland area were also referred for management of their blood disorders.

Table 1 shows the patients referred, with age range and sex. Of the 83 patients with Hodgkin's disease all save 3 had splenectomy as part of staging laparotomy. Of these three patients, one had a very large spleen with hypersplenism and the operation was both diagnostic and therapeutic; one with previously treated Stage IA Hodgkin's disease had a laparotomy to remove a staghorn calculus of the left kidney and was found at operation to have Hodgkin's tissue in and outside the kidney, involving the spleen; and the third, with previously irradiated localized Hodgkin's disease of the neck developed fulminating thrombocytopenic purpura, splenectomy being performed therapeutically, and the spleen was involved in Hodgkin's disease[11].

Of the eight patients with non-Hodgkin's lymphoma, three had severe blood changes of hypersplenism, including auto-immune haemolytic anaemia and thrombocytopenia, and two further patients had considerable abdominal pain due to large spleen size. The remaining three had removal of a large spleen in the course of a diagnostic laparotomy.

All 11 patients with chronic granulocytic leukaemia had splenectomy early in the benign phase of their disease, in an attempt to reduce later symptoms arising from a massive spleen in the malignant phase. One patient had the spleen removed rather earlier than usual, because of recurrent massive splenic infarction, even when the platelet count was controlled.

The patients with haemolytic anaemia were divided into those with hereditary haemolysis (all cases of hereditary spherocytosis) and those with acquired auto-immune haemolytic anaemia (AIHA). In the hereditary group of 21 patients, no medication such as steroids was given before the operation, and the age group at operation was mainly much younger than the other patients, although there were also several adults. The eight cases with AIHA had had a trial of immunosuppressives, usually steroids and azathioprine, and came to splenectomy after failure or relapse on these drugs. Seven had radio chromium (^{51}Cr) studies before splenectomy, indicating increased splenic sequestration. This group consists solely of patients in whom auto-immune haemolysis was the only evidence of haematological disease—several of the patients described later with hypersplenism had AIHA as part of their haematological picture.

Similarly, the 34 patients with auto-immune thrombocytopenic

Table 1 *Patients having elective splenectomy for haematological conditions*

Disease/condition	No. of patients	M	F	Age range (years)
Hodgkin's disease	83	45	38	6–70
Non-Hodgkin's lymphoma	8	4	4	30–61
Chronic granulocytic leukaemia	11	7	4	20–47
Haemolytic anaemia				
Hereditary spherocytosis	21	12	9	2–60
Auto-immune haemolytic anaemia	8	2	6	12–69
Auto-immune thrombocytopenia	34	12	22	3–73
Hypersplenism				
Cystic spleen	4	1	3	11–51
Gaucher's disease	4	1	3	1–15
Felty's syndrome	3	1	2	41–62
Portal hypertension	6	4	2	6–73
Myelofibrosis	2	2	0	45–62
Hairy cell leukaemia	1	1	0	54
Total	185	92	93	

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Table 2 *Immediate postoperative morbidity after splenectomy*

Disease/condition	No. of patients	Days in hospital (mean)	Number of infections			Thrombo-embolism	Haemorrhage	Deaths
			Chest	Wound	Other			
Hodgkin's disease	83	9·1	11	4	3*	2	1	0
Non-Hodgkin's lymphoma	8	13·6	4	1	1†	—	—	0
Chronic granulocytic leukaemia	11	8·9	1	1	—	—	1	0
Hereditary spherocytosis	21	8·2	3	1	—	—	1	0
Auto-immune haemolytic anaemia	8	8·8	—	—	1‡	—	—	0
Auto-immune thrombocytopenic purpura	34	9·1	3	1	—	—	—	0
Hypersplenism								
Cystic spleen	4	10·0	—	—	—	—	—	0
Gaucher's disease	4	13·3	—	1	—	—	—	0
Felty's syndrome	3	9·7	1	—	—	—	—	0
Portal hypertension	6	8·7	1	1	—	—	—	0
Myelofibrosis	2	—	—	—	—	—	1	2
Hairy cell leukaemia	1	10·0	—	—	1§	—	—	0
Total	185		24	10	6	2	4	2

* One subphrenic abscess, two urinary tract infections; † bacteraemia; ‡ urinary tract infection; § herpes simplex with severe bacterial secondary infection

purpura had splenectomy only when there was relapse or failure to maintain adequate haemostasis without such large doses of immunosuppressives as to produce unacceptable side-effects. Two of the patients, both elderly, had auto-immune thrombocytopenia secondary to chronic lymphocytic leukaemia. Twelve of the patients with severe thrombocytopenia had platelet concentrate just before the operation to allow the anaesthetist safe access to the airway, and to 'cover' opening of the abdominal wall and splenic mobilization.

A group of 20 patients had hypersplenism—all had considerable reduction in haemoglobin, white blood counts and platelets, some overt haemolytic anaemia, and all had considerable splenomegaly. Four had Gaucher's disease (three of the adult variety), three had Felty's syndrome and six had portal hypertension with normal liver function (four due to presumed neonatal umbilical vein infection). One patient with hairy cell leukaemia and two with myelofibrosis had surgery because of symptoms from thrombocytopenia and anaemia. Four patients had splenic cysts—one congenital, one traumatic, one was initially considered to be traumatic but the splenunculus was also cystic, and one was a haemangioma—all, somewhat unusually, producing hypersplenism.

Operative procedure

In staging laparotomy, wedge biopsies of both lobes of liver, and of para-aortic and coeliac nodes were obtained. Other procedures were performed where these were indicated clinically.

The postoperative complications were recorded and their severity judged partly from the case record and nursing notes, and partly by the length of stay in hospital after operation. If hospital stay was longer than the median length by more than 2 days because of infection this was regarded as major infection. Thrombo-embolism was detected as described by us previously[12].

Results

Operative morbidity

Although length of stay in hospital has been used as a rough guide to morbidity after operation, other factors influenced the length of stay, such as geographical considerations and social circumstances. However, the mean postoperative stay was acceptably short, considering that many of the patients were ill pre-operatively. *Table 2* shows the postoperative complications of infection, thrombo-embolism and haemorrhage, in the first month after surgery.

Of the 24 chest infections, 4 were major, that is prolonging hospital stay. The 10 wound infections were all minor and responded to routine local care. There were three other major infections; a subphrenic abscess which manifested itself after the start of cytotoxic chemotherapy for Hodgkin's disease; one postoperative bacteraemia in a man with non-Hodgkin's lymphoma with a white blood count pre-operatively of $<1{\cdot}0\times10^9/l$; and a severe secondary bacterial infection in a herpes simplex lesion in the patient with hairy cell leukaemia—in each of these the underlying disease was the main contributor to the infection.

Thrombo-embolism occurred in two patients with Hodgkin's disease, one the man with the subphrenic abscess. Four patients had postoperative haemorrhage requiring re-laparotomy. Only one of these patients had a low platelet count at operation; he had myelofibrosis and massive splenomegaly. He had a further haemorrhage after the second laparotomy and the decision was made not to attempt further surgery; he died on the second day after splenectomy. The other three patients made an uninterrupted recovery.

The only other postoperative death occurred from a ruptured aortic aneurysm in a man with myelofibrosis on the sixth day after splenectomy.

Relapse of disease

The incidence of relapse of the haematological disease is shown in *Table 3*. In the malignant diseases, splenectomy was used as either a diagnostic or staging procedure, or to deal with the present or later problems of hypersplenism, and was not expected to exert much influence on the relapse or natural development of the disease.

Twenty patients with Hodgkin's disease relapsed, eleven of whom had standard chemotherapy as first-line management, and most of these patients had aggressive disease. In the other nine, one had total nodal irradiation and the other eight had mantle radiotherapy. In retrospect, four of these eight patients had minor systemic symptoms which may have made their true initial clinical Stage IIB. Two of the patients with non-Hodgkin's lymphoma relapsed late after first-line chemotherapy, but responded well to a second course of chemotherapy.

Of the haemolytic anaemias, none of the patients with hereditary spherocytosis had further haematological problems. Of the auto-immune haemolytic anaemias, four of the eight patients relapsed, one requiring no treatment, two requiring a much smaller dose of immunosuppressive intermittently, and one having a major, but transient, relapse 6 years after splenectomy.

Thirteen of the thirty-four patients with auto-immune thrombocytopenia relapsed, most within a few months; seven had a mild relapse requiring no treatment, and a further four had symptoms controlled with much less immunosuppression than before splenectomy. Two elderly patients (one with auto-immune thrombocytopenia secondary to chronic lymphocytic leukaemia) relapsed with major haemorrhagic symptoms, 2 and 3 months after splenectomy and both died of haemorrhage.

Table 3 *Relapse of disease after splenectomy*

	No. of patients	No. relapsing	Time to relapse (months)	Comments
Hodgkin's disease	83	20	4–83	11 had chemotherapy 9 had radiotherapy
Non-Hodgkin's lymphoma	8	2	40–95	Both had had chemotherapy
Chronic granulocytic leukaemia	11	Not applicable		
Hereditary spherocytosis	21	—	—	
Auto-immune haemolytic anaemia	8	4	1–72	3 were minor relapses
Auto-immune thrombocytopenia	34	13	1–168	11 were minor relapses
Hypersplenism				
Cystic spleen	4	1	80	Metastatic haemangiosarcoma
Gaucher's disease	4	1	1	Infantile Gaucher's disease
Felty's syndrome	3	1	48	Agranulocytosis recurred
Portal hypertension	6	3	23–72	Bleeding from oesophageal varices
Myelofibrosis	2	—	—	
Hairy cell leukaemia	1	1	5	Recurrence of haemorrhage

Development of late complications of splenectomy

Infection. In the whole series, there were four examples in three patients of overwhelming infection of postsplenectomy type (OPSI). Two cases were presumptive and fatal. The first was in a 10-year-old boy who had a splenectomy at the age of 5 for severe recurring auto-immune thrombocytopenia. He had stopped postsplenectomy penicillin and died, in England, within hours of the onset of diarrhoea before reaching hospital. The coroner's verdict was overwhelming infection, but no organism was isolated.

The second was a girl who, at the age of 8, had had a splenectomy for staging of Hodgkin's disease, which was treated with chemotherapy. At the age of 11, in remission and off both cytotoxic drugs and prophylactic penicillin, she developed meningococcal bacteraemia with meningitis, from which she made a complete recovery. In September 1984, at the age of 17, and 9 years after the splenectomy, she presented with diarrhoea, cardiovascular collapse, developed disseminated intravascular coagulation, and died within hours of hospital admission, despite broad-spectrum antibiotics, steroids and supportive measures. Blood culture before antibiotics was sterile, and there was no evidence of Hodgkin's disease at autopsy.

The third patient, a boy, aged 15, who had had a splenectomy for severe, recurrent auto-immune thrombocytopenic purpura 6 months earlier and refused to take phenoxymethyl penicillin, was admitted with a febrile respiratory illness and recurrence of mild purpura. He had serological evidence of recent influenza B infection; with pneumococcus recovered from blood culture and minor recurrence of thrombocytopenia. He recovered rapidly.

Many other late infections were recorded, related to the underlying malignant haematological disease and/or its treatment—in Hodgkin's disease patients, herpes zoster, pneumocystis carinii infestation, and bacteraemia during chemotherapy; in leukaemia, bacteraemia. Several patients had recrudescence of previously existing infections, for example bronchiectasis, tonsillitis, sinusitis and two had much later episodes of agranulocytosis with infection. Splenectomy seemed to have no effect on the severity of this group of infections.

Late deaths since splenectomy

Thirty-four patients have died since splenectomy. *Table 4* sets out the causes of death. It can be seen that a significant number, probably 27, of the deaths were related to the underlying disease. Ten patients died of Hodgkin's disease, relapsing after primary treatment. Review of these patients showed rapid relapse of aggressive disease after apparently adequate chemotherapy in seven, and one developed terminally acute myeloid leukaemia. In two cases, there was some suspicion in retrospect that minor systemic symptoms were enough to warrant initial staging as IIB, so that chemotherapy, not radiotherapy, should have been first-line management. Both relapsed systemically—that is laparotomy had not missed local disease which recurred. Non-Hodgkin's lymphoma was the case of death in two of the patients treated initially for auto-immune haemolytic anaemia, and underlying collagen disease (SLE) in two elderly patients previously treated for Felty's syndrome. Only 2 late deaths of the 185 occurred as a probable result of the splenectomy.

Discussion

The present series has the advantage of comprising a substantial number of unselected patients of all ages, presenting to the hospitals of an area, thus allowing uniformity of surgical and haematological acute care and prolonged follow-up. It gives a realistic assessment of the use and risks of the operation in these patients.

Indications for splenectomy

In Hodgkin's disease, imaging techniques have greatly improved over the 15 years, but there is not yet a foolproof non-invasive way of delineating small deposits of the disease in the abdomen, especially the spleen[13]. At present, in young adult patients with disease apparently confined above the diaphragm, without a large mediastinal mass or systemic symptoms, splenectomy is still necessary in our view, although we would agree that in children, all other disease but Stage IA requires chemotherapy, so that splenectomy can be avoided[14]. One difficulty is in being certain that minor general symptoms are not significant systemic 'B' symptoms and this problem has been given insufficient attention in assessing clinical staging. Recently the British National Lymphoma Investigation has produced a prognostic index[10] to predict patients with early stage disease but a poor prognosis who would require chemotherapy as first-line treatment and this will further reduce the number of staging laparotomies.

The patients with non-Hodgkin's lymphoma and large spleens, having diagnostic and/or therapeutic splenectomy have responded well to subsequent chemotherapy despite initial severely reduced white blood cell counts[15]. Although there is a higher incidence of thrombo-embolism postsplenectomy in patients with massive splenomegaly[12], the results in our small group seem to justify carrying out splenectomy in these patients. Severely ill patients returned to normal health, and, even in the two who relapsed, further chemotherapy has produced long-term complete remission. An additional benefit of splenectomy in lymphomas may be toleration of higher dose intensity of cytotoxic chemotherapy[16–19] although this has been disputed[20].

In chronic granulocytic leukaemia, the removal of the spleen routinely has been shown not to prolong life[7,8] although it may

Table 4 *Deaths late after splenectomy*

Disease/condition	No. of patients	No. of deaths	Age at death	Cause of death	
Hodgkin's disease	83	10	25–70	Relapse of Hodgkin's disease	9
				Acute myeloid leukaemia	1
Non-Hodgkin's lymphoma	8	0	–		
Chronic granulocytic leukaemia	11	6	24–49	Malignant transformation	6
Hereditary spherocytosis	21	1	75	Carcinoma of rectum	1
Auto-immune haemolytic anaemia	8	2	33–60	Non-Hodgkin's lymphoma	2
Auto-immune thrombocytopenia	34	6	10–75	Myocardial infarction	2
				Road traffic accident	1
				Infection (not proven)	1
				Haemorrhage	2
Hypersplenism					
Cystic spleen	4	1	49	Haemangiosarcomatosis	1
Gaucher's disease	4	1	1	Gaucher's disease	1
Felty's syndrome	3	2		Systemic lupus erythematosis	2
Portal hypertension	6	1		Myocardial infarction	1
Myelofibrosis	2	2		Postoperative haemorrhage	1
				Ruptured aortic aneurysm	1
Hairy cell leukaemia	1	1		Leukaemia	1
	185	33			

improve the speed of engraftment in later bone marrow transplant[21].

In considering the non-malignant diseases for which splenectomy is performed, patients with auto-immune thrombocytopenia should be considered only if the clinical condition is severe, if bleeding, especially mucosal haemorrhage, recurs whenever immunosuppressive drug dosage is reduced to an acceptably low level, and particularly if it occurs in adults. However, although there was a recurrence rate of more than one-third of all patients, in only two was splenectomy unable to prevent death from haemorrhage and most patients had only very minor symptoms on recurrence, requiring much less, or no, immunosuppressive therapy. Almost all remarked on general improvement in health. This, and the removal of the risks of long-term immunosuppression, are important, but difficult to quantify.

In hereditary spherocytosis, the ideal, hallowed by time, is to let the child reach at least primary school age (and, so, reach 'adult' humoral immunological status) before splenectomy. However, circumstances such as repeated haemolytic crises, often following minor infection, may dictate earlier splenectomy. In our patients, the severity of the condition varied from one family to another and bred true. Complications in the biliary tract may be severe and, in our series, splenectomy was undertaken in some adults either combined with, or to prevent, biliary surgery because of pigment gallstones.

Although half the patients with auto-immune haemolytic anaemia relapsed, in only one was there a late severe relapse with agranulocytosis and thrombocytopenia; and that patient's splenectomy had been carried out initially for fulminating haemolysis. Thus, splenectomy was well worthwhile in this group of patients, especially if they had clear evidence of excess splenic sequestration of red blood cells. The later development of non-Hodgkin's lymphoma may have been related to immunosuppression before splenectomy (*Table 4*).

Hypersplenism includes a miscellany of diseases. The cystic spleens were probably congenital in two patients and the seat of haemangioma in the third which later became sarcomatous with metastases. All patients had their significant symptoms of hypersplenism relieved. Gaucher's disease, with gross splenomegaly and severe depression of the blood count, is recognized as a poor risk for splenectomy, especially in the infant form of the disease. However, our experience has been encouraging, with three of the four patients living normal lives after operation. Juvenile portal hypertension may now be dealt with by vascular surgery to relieve the hypertension rather than by splenectomy.

The patients with Felty's syndrome treated by splenectomy were a small minority of such patients, and were selected because of the severity of their symptomatic hypersplenism, especially when causing severe systemic infections. Although two eventually died of their underlying collagen disease (SLE), it was several years after splenectomy, and operation was well worthwhile.

Precautions against infection after splenectomy

Our policy in the whole series was to give phenoxymethyl penicillin to children and adolescents for 2 years after splenectomy. In addition, in the last 2 years of the study, patients of all ages were given pneumococcal polysaccharide vaccine pre-operatively. The patient and/or the parents and the general practitioner were warned about the serious significance of acute illness. We think it probable that OPSI occurred four times in three patients (1·6 per cent), two of whom died: two patients had completed their 'course' of prophylactic penicillin and one adolescent had refused to take it.

There has been no published proof of clear benefit from penicillin prophylaxis (although most of the organisms causing OPSI are sensitive) and there are problems with compliance, especially in adolescents. Although pneumococcal vaccine can generate antibodies in asplenic subjects with non-malignant conditions[22], the antibody response in patients with Hodgkin's disease, especially after therapy, is impaired[23,24]. Even in those patients who develop antibodies, they may not have opsonic activity to prevent infection[25,26]. Although a decade ago, Chilcote *et al.*[27] suggested evaluating prospective prophylactic penicillin and vaccines after splenectomy in children with Hodgkin's disease, there are no prospective studies of the benefit of pneumococcal vaccine in splenectomized patients. Similarly, although antibody response to meningococcal vaccine is known to be impaired in treated lymphoma patients[28] no results are available of its efficiency. It may well be that using such prophylaxis lulls the medical staff into a false sense of security.

The incidence of OPSI has not been well quantified, the difficulty being to separate the effects of splenectomy from the effects of the disease being treated. For instance the occurrence of infection is frequently related to neutropenia induced by chemotherapy or the debility of advanced or recurrent Hodgkin's disease, so that the role of splenectomy is not clear[29–33]. Although reporting bias has undoubtedly exaggerated the dangers of OPSI, the risk is present, and deaths have been reported many years after the operation[34,35]. This great concern has resulted in attempts to preserve splenic tissue whenever possible[36,37] and this is now technically more feasible.

While maintaining a constantly critical attitude to every splenectomy, especially in children, the threat of OPSI should not prevent the operation where it is necessary for diagnosis or for the patients' well-being. The most important safeguards are a high index of suspicion by medical staff in patients at risk, and education of relatives, general practitioners and emergency hospital staff in rapid appropriate management of the ill asplenic patient.

Acknowledgements

We wish to thank our many clinical colleagues who referred patients to us.

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Paper accepted 8 December 1986

Br. J. Surg. 1987, Vol. 74, May, 358–361

Carcinoid tumours of the rectum and anus

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Carcinoid tumours of the anorectum comprise only 0·1 per cent of all rectal tumours. Their behaviour and treatment are still debatable. We identified 35 cases from the records of St Mark's Hospital; 31 were benign and 4 were malignant. Benign tumours were of three distinct histopathological patterns. All benign tumours were cured by local treatment. Malignant tumours can be identified clinically; the only consistent microscopic feature was invasion of the muscularis propria. All patients with malignant tumours died, despite radical surgical treatment; lymph node metastases were invariably present in the operation specimens. Because radical treatment for malignant carcinoid tumours of the anorectum is largely unsuccessful, a flexible surgical approach is advocated.

Keywords: Carcinoid tumours, rectum, anus, APUD

Carcinoid tumours of the anorectum are rare. Their incidence has been estimated at 0·14 per cent of all rectal tumours and 0·7 per cent of malignant rectal tumours[1]. Because of this rarity several aspects of the management of these tumours remain controversial. Diagnosis may be delayed because of failure to recognize their morphological characteristics. Histological appearance may not reflect their biological behaviour. Several substantial series and literature reviews[1–3,5–7,9] have provided no clear concensus on the type of further treatment that should be offered after initial diagnostic methods have revealed an (apparently) benign carcinoid, or whether local or radical treatment should be advised for malignant ones. To help resolve these clinical dilemmas and to assess the clinical features and pathological nature of these rare tumours the cases treated at St. Mark's Hospital since the diagnosis was first recorded in the pathological records of the hospital in 1936 have been reviewed.

Patients and methods (*Figure 1*)

We identified 35 patients with carcinoid tumours of the anorectum seen at St. Mark's Hospital during the period 1936–1983 from the pathological records. There were 19 men and 16 women with an average age at presentation of 47·7 years (range 24–84 years). Their clinical records were examined with special reference to presenting symptoms, associated conditions, macroscopic appearance of the lesions and methods of diagnosis and treatment with the outcome. All available histology slides were studied with respect to morphological patterns, evidence of malignancy and evidence of complete removal in relation to results of initial treatment. Where blocks were available Grimelius' argyrophyl stains, Masson–Fontana argentaffin stains and neurone-specific enolase immunoperoxidase stains were performed.

Results

Clinical features (Tables 1 *and* 2)

There were 31 benign lesions and 4 exhibited malignant behaviour (*Table 1*).

Benign lesions. All patients with benign lesions presented with symptoms due to a wide variety of associated anorectal conditions (*Table 2*), but in none were the symptoms due to the carcinoid tumour. All were found incidentally during management for the presenting conditions. There were 24 tumours discovered by routine out-patient sigmoidoscopy. Their appearances were variable, ranging from a red area to a polypoid form, although most were protuberant to some degree. Only three were described as submucosal, and of these only one was noted to be yellow: this last case was the only patient whose carcinoid tumour was identified correctly from its macroscopic appearance. The lesions were concentrated mainly in the lower and middle thirds of the rectum.

In addition benign carcinoids were found incidentally in operative specimens removed for other reasons: one patient for an adenocarcinoma of the rectum; one patient for combined ulcerative colitis and adenocarcinoma; and one patient for total (ulcerative) colitis. Two extrarectal carcinoids were included in the series. One was found in a long-standing recurrent anal fistula and the other in a postrectal cystic teratoma.

Malignant lesions. In contrast to the benign cases, three of the four patients presenting with malignant carcinoids had symptoms directly attributable to the tumour. Three patients complained of rectal bleeding of 3 months to 2 years duration. On sigmoidoscopy, two of the three symptomatic patients were

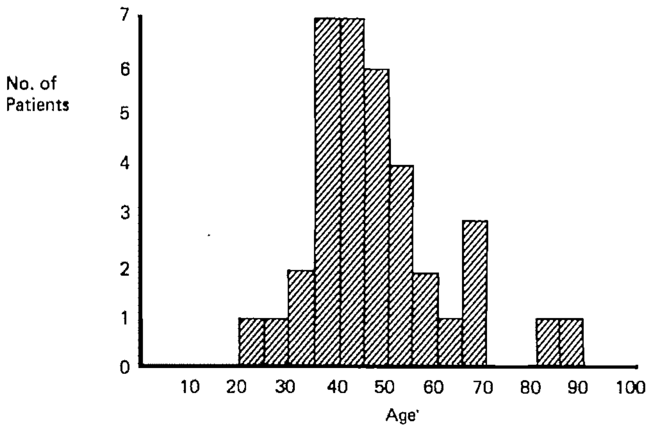

Figure 1 *The age distribution of the patients who had a carcinoid tumour of the anorectum. There were 35 patients, 19 men and 16 women*

Table 1 *The clinical features of carcinoid tumours of the anorectum*

	Benign (31)	Malignant (4)
Symptoms	None	All
Size	Small < 1·0 cm	Large 3 > 2·0 cm
Morphology	Non-specific	Ulcerated
Outcome	Cure (by local treatment)	Fatal (despite radical surgery)

Table 2 *Associated features of patients with benign carcinoid tumours of the anorectum*

Associated conditions	
Haemorrhoids	15
Fissure-in-ano	6
Carcinoma of rectum	4
Colitis	3
Fistula-in-ano	3
Metaplastic polyp	2
Miscellaneous	
Adenoma	1
Anterior mucosal prolapse	1
Fibrous and polyp	1
Diverticulitis	1
Incontinence	1
Post-rectal teratoma	1

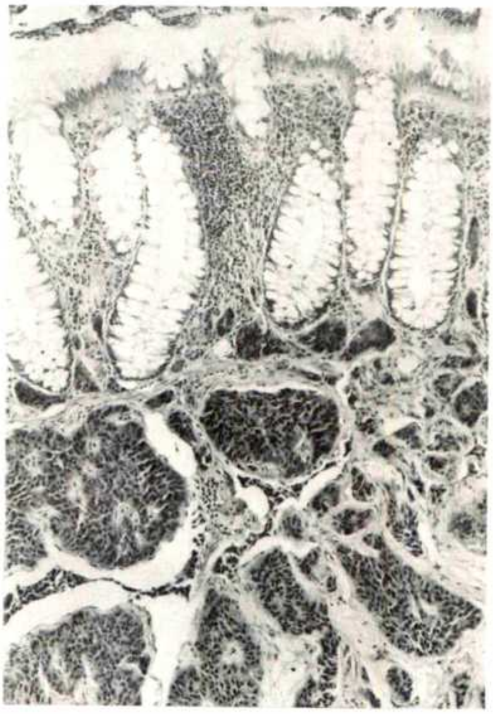

Figure 2 *Type 1 carcinoid tumour, benign: note the predominant solid nests of tumour cells. The microphotograph also shows nests of tumour present in the lamina propria of the overlying mucosa, which remains intact*

found to have ulcerating lesions with surface bleeding, and were thought to have carcinomas from their macroscopic features: the other patient had a small pedunculated lesion which was ulcerated and bleeding from its apex. The fourth patient also had symptoms of bleeding, but had a synchronous rectal adenocarcinoma which was considered the source of the symptoms, as well as being the cause of the surgical treatment (rectal excision). None of the benign or malignant tumours caused symptoms of the 'carcinoid syndrome', even when liver metastases were present.

Pathology

Benign lesions (n = *31*). Of the 31 cases, 28 had histological material suitable for detailed examination. As a result it was possible to allocate the tumours to one of three distinct patterns.

(*i*) *Type 1* n = *10* (Figure 2): These were similar to classical midgut carcinoids and were composed of solid nests of tumour cells with some trabecular cords at the periphery. Tubulo-acinar differentiation was occasionally seen. Three of these tumours displayed argyrophilia and argentaffinity.

(*ii*) *Type 2* n = *11* (Figure 3): These showed a pronounced ribboning pattern, often with an anastomosing configuration and a prominent vascular network. No argyrophilia or argentaffinity was found in these tumours.

(*iii*) *Type 3* n = *7*: These had a mixed pattern with features of both types 1 and 2. No argyrophilia or argentaffinity was exhibited by these tumours.

In addition to the major features enabling their classification into the three distinct types, all the tumours exhibited a fibroblastic stromal reaction, most marked in four of the type 1 cases. Twelve tumours showed plentiful smooth muscle incorporation into the stroma, but this was not typical for any tumour type; however, it was most marked in the small (< 1 cm) lesions closely applied to the muscularis mucosae. In all 28 cases, the overlying mucosa was intact: in 19 cases the mucosa was infiltrated by carcinoid cells. All the tumours were submitted to additional examination by the neurone-specific enolase technique; all were positive, supporting the diagnosis of carcinoid.

Malignant lesions (n = *4*) Figure 4. The only consistently reliable histological feature of malignancy was invasion of the muscularis propria. A marked fibroblastic reaction and incorporation of smooth muscle into the stroma were found frequently in benign non-aggressive lesions. Involvement of the mucosa and submucosa were found in benign lesions, but consistent with the macroscopic clinical observations, ulceration of the mucosa and necrosis were only shown by the malignant tumours. Cytological features consistent with malignancy such as a high mitotic index, pleomorphism, hyperchromatism and abnormal chromatin patterns were shown by three of the malignant tumours but were absent from case 3. All four malignant tumours showed areas of ribboning, increased vascularity and anastomotic configuration as found in type 2 benign lesions, but no traces of type 1 morphology were present. Involvement of lymph nodes by metastatic carcinoid tumour was invariably present in the malignant cases.

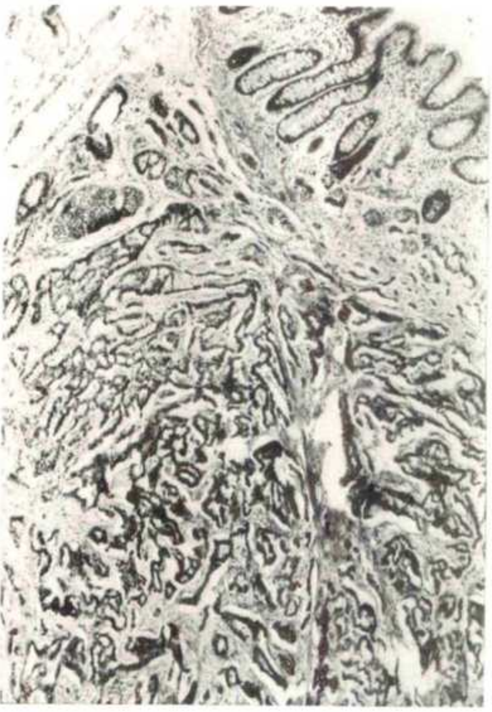

Figure 3 *Type 2 carcinoid tumour, benign: note the typical ribboning pattern with an anastomosing configuration. Again, the overlying mucosa remains intact although it contains small ribbons of carcinoid tumour*

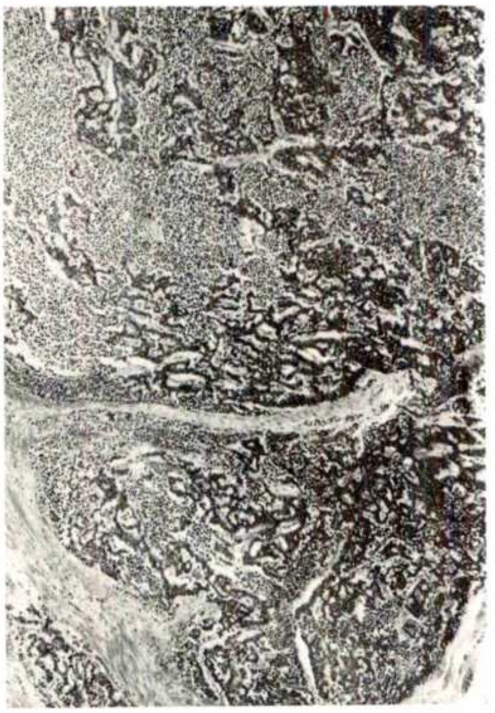

Figure 4 *Malignant carcinoid of rectum: note the malignant carcinoid cells in the lower left corner which are infiltrating the muscularis propria (see text). Areas of anastomosing ribboning pattern are present which are characteristic of benign type 2 carcinoid tumours, but there are also areas of solid undifferentiated tumour*

Treatment

Benign lesions. Because only one case was diagnosed correctly by its macroscopic appearance, treatment was fortuitous. In 14 cases, initial treatment was by biopsy only, and in 7 cases excision was known to be incomplete. Six cases were handled by biopsy-excision, and in two of these excision was not confirmed to be complete by pathological examination. Four lesions were removed by snare-diathermy, and in two of these excision was incomplete. Thus 46 per cent of the benign tumours were incompletely removed by their initial management procedures.

Follow-up ranged from 0 to 29 years, with a median interval of 15 months. In spite of the high ratio of incomplete to complete removal at the first treatment, recurrence of benign tumours was a rare event. Of the cases treated by biopsy alone there were two recurrences, one after 4 months (type 3 lesion), and one after 11 months (type 1 lesion); both were handled by local excision and had not recurred 5 and 29 years later respectively. The patients treated by biopsy-excision, snare-diathermy or by wide surgical removal for accompanying lesions had no recurrence.

Malignant lesions. Of the four patients, three were treated by radical rectal excision at the first treatment. One patient with a small pedunculated lesion was treated initially by surgical submucosal excision; early local recurrence was noted 3 months later, and was treated promptly by radical rectal excision. After rectal excision all four patients were found to have positive involved nodes in the operation specimen. One patient had hepatic metastases at the time of the surgery. All four patients with malignant disease died. Case 1, who had an advanced tumour and hepatic metastases, died of heart failure in the immediate postoperative recovery period. Cases 2 and 3 died of histologically confirmed disseminated carcinoid tumour 4 years 7 months and 2 years 9 months respectively after synchronous combined excision of the rectum. Case 4, with synchronous adenocarcinoma and malignant carcinoid of the rectum, died of disseminated malignancy 7 years 3 months after radical rectal excision: although no autopsy was allowed, the facts that lymphatic nodal metastases were of carcinoid tumour and the extended postoperative survival time, have caused death to be attributed to metastases from the carcinoid tumour rather than the synchronous adenocarcinoma (which was a Dukes' B lesion).

Discussion

This study confirms the rarity of these tumours[1,2,8], only 35 cases being recorded during a 49 year period when 5789 patients with rectal carcinoma were diagnosed at the same institution.

The clinical features of the tumour are not specific enough for the diagnosis to be made at the first examination. The average age at presentation (47·7 years) was lower than for rectal carcinoma (62·3 years in men and 60·7 years in women) but comparable to other reported series[2,3,5,8-10]: this series also confirms the wide range of age at presentation (24 to 84 years) noted by others[10]. The sex distribution was almost equal.

The diagnosis of rectal carcinoid is impossible to establish by its morphological characteristics seen on endoscopy. In contrast to ileal or appendicular carcinoids, yellow coloration is not a feature of rectal carcinoids, and in only 1 of our 35 cases was a correct diagnosis made by the visual appearance on sigmoidoscopy. Although most of the benign carcinoids presented a raised or polypoid appearance, there was one which was described as an 'area of mucosal discoloration or blush' by the observer. In the malignant cases when an ulcerated appearance or evidence of spread had indicated invasive potential the tumour was considered to be a carcinoma until the biopsy revealed the true diagnosis.

Even when the tumour had given rise to massive hepatic liver secondaries, the carcinoid syndrome was absent: Gabriel and Morson[4] and Peskin and Orloff[10] have discussed the absence of secretory endocrine properties by rectal carcinoids and have drawn attention, with others[11] to the rarity of endocellular cytoplasmic granules in these tumours.

The biopsy examination is the one certain method to establish the diagnosis of 'carcinoid' although there are serious difficulties in differentiating between the benign and malignant forms. It is apparent from this series that many of the smaller ($<1·0$ cm diameter) lesions were simply picked off with biopsy forceps at presentation. We agree with Morton and Johnstone[8], and others[5,10] that the distinction between a benign and a malignant carcinoid tumour cannot be made with certainty by the histopathologist unless either the entire tumour is sent for examination ('total excision-biopsy') or the tissue bite is deep enough to establish whether the muscularis propria is invaded. Neither a fibroblastic reaction, incorporation of smooth muscle in the stroma, infiltration of the mucosa and submucosa or cytological changes usually associated with malignancy are able to indicate invasive potential by a carcinoid tumour: our findings are in agreement with others[6,8] that only invasion of the muscular propria is a consistently reliable guide to the malignant nature of a carcinoid tumour.

The diameter of the tumour has been advanced as a guide to its biological nature[5,10]. It has been suggested that tumours $>2·0$ cm diameter can be regarded as malignant. While it is true that most malignant carcinoids are $>2·0$ cm diameter, malignant carcinoids of smaller size occur, as has been found by Jackman[12], Morton and Johnstone[8] and Caldarola[5]. One of the malignant carcinoids in this series was much less than 2·0 cm diameter, and there were lymph node metastases when a rectal excision was carried out 3 months after an initial attempt at cure by local excision. It would appear unsafe to assume that a carcinoid tumour with size $<2·0$ cm was benign.

There was one helpful clinical feature in our series that has not been drawn attention to previously. None of the benign carcinoids presented with symptoms relating to the tumour, presumably because the overlying mucosa was intact. By contrast, all our malignant carcinoids were symptomatic, bleeding being a prominent symptom. It would be safe, in our view, to conclude that a carcinoid tumour was benign if at presentation it was both asymptomatic and $< 2\cdot0$ cm diameter, although final confirmation by biopsy of appropriate depth would still be necessary to confirm that the muscularis propria was not invaded.

The importance of obtaining as many facts as possible to establish that a carcinoid tumour is benign is brought out in the management of these tumours. Although in the past, as in this series, many of the tumours were incompletely excised by the initial diagnostic procedure, local recurrence is rare[7,10]. There were only two local recurrences after locally incomplete excision in this series, and Tumacder *et al.*[7] recorded no recurrence in 23 asymptomatic tumours $< 1\cdot0$ cm in diameter treated by punch-biopsy only. In our series we too have found the absence of symptoms a reliable guide to the benign nature of a carcinoid tumour. Therefore, local recurrence need not be regarded as indicating malignancy (and precipitating resort to radical surgical intervention) providing the clinician is certain that the original tumour was benign. Ponka and Walke[3] have shown that further local excision for a benign carcinoid that has been incompletely excised can achieve cure.

This series confirms that malignant rectal carcinoids carry a very poor outlook for cure. All four cases in this series had lymph node or disseminated metastases when radical surgery was performed. All four patients died with disseminated metastases and in one patient who died soon after radical surgery liver metastases were present at operation. Bates[2] collected 41 cases of malignant rectal carcinoids, of which only 4 survived more than 5 years. It is questionable whether radical surgery can be justified as the only way to treat a malignant carcinoid, when cure is so unlikely. For accessible lesions, it might be justified to attempt wide local removal in patients who are > 65 years old at presentation on the grounds that surgical intervention is palliative rather than curative in most cases and that patients can survive for many years with metastases from carcinoid tumours (which will not cause the carcinoid syndrome if the primary is in the rectum). For tumours of the upper and middle third of the rectum an anterior resection would appear to be the treatment of choice as combining effective palliation by removal of local and lymphatic tumour deposits with the greatest chance of cure until radiation or chemical treatments can be shown to be effective for malignant carcinoid tumours. For the occasional young patients (< 40 years old) radical surgery seems still to be their best chance of cure, however small, but every effort must be made to avoid a permanent colostomy because the outlook is so poor.

Acknowledgements

We are grateful to the past and present staff of St. Mark's Hospital for allowing us to study their patients.

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Paper accepted 3 November 1986

Announcement

The Association of Surgeons in Training

Membership of the Association is open to all Senior Registrars holding accredited posts in general surgery, urology, paediatric surgery, plastic surgery, neurosurgery, and cardiothoracic surgery, and all registrars in the same specialties who are two years post-fellowship, subject to application. The association represents the views of members on all matters relevant to surgical training besides having scientific and social functions.

If you are not a member please contact the secretary, Simon Ambrose, Department of Surgery, Clinical Teaching Block, General Hospital, Steelhouse Lane, Birmingham B4 6NH, UK, for details of membership, local representatives and forthcoming meetings. The next AGM will be held in Liverpool on 2–4 September 1987.

Br. J. Surg. 1987, Vol. 74, May,
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Management of colovesical fistula

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The clinical presentation and management of 24 patients treated for colovesical fistula were reviewed. It is concluded that an aggressive investigative approach in the management of patients with suspected colovesical fistula is rewarding. Cystoscopy and barium enema appear to be the most useful investigative tools. Once found the fistulae should be managed surgically. Radical excision of the sigmoid colon with primary anastomosis is the treatment of choice and is accompanied by no mortality and a very low complication rate.

Keywords: Colovesical fistula, cytoscopy, barium enema

Colovesical fistula can present diagnostic difficulty as the pathology is colonic but the presenting symptoms suggest a problem with the urinary tract. These are often related to persistent lower urinary tract infections but complications such as pyelonephritis may occur. The fistulae are usually secondary to diverticular disease of the colon; malignant disease is a much less frequent cause. The condition is treatable by surgery in the majority of cases but confusion regarding the investigations and management still exists. It seemed pertinent to review a series treated over a relatively short time.

Patients and methods

Patients

The presenting features, investigation, management and aetiology of fistulae presenting over a 5 year period in 24 patients (18 men and 6 women), age range 30–78 years, were determined from a restrospective analysis of the case records.

The patients were investigated because symptoms had been present for longer than 3 months. Twenty patients presented with history of recurrent and persistent 'cystitis' which had been refractory to antibiotic treatment prescribed by the general practitioner. Pneumaturia was present in 10 patients and 2 gave a history of haematuria. Bowel symptoms were the chief presenting symptoms in only four who also admitted to urinary symptoms on direct questioning. Physical examination revealed a tender mass in the left iliac fossa in 13 cases.

Investigations

Culture of midstream specimens of urine grew faecal organisms in 17; sterile pyuria was found in the remainder. Barium enema examination was performed in all patients and results were abnormal in all instances. The presence of a fistula was demonstrated in twelve and inferred in two because of the entry of barium into the bladder. In three patients, colonic tumour was demonstrated. In the remainder there was evidence of diverticular disease of the colon. Intravenous urogram was performed in all patients, the upper tracts all being normal. In 12, there were abnormalities in the bladder: a space occupying lesion in 6, gas in 3 and extrinsic compression in 3 cases.

All patients underwent examination under anaesthesia, cystoscopy and sigmoidoscopy; examination revealed a mass in 20. On sigmoidoscopy a stricture was found in one, a definite tumour in two and in four pus was seen in the lumen of the bowel. Cystoscopy typically revealed an inflamed and oedematous area over the dome of the bladder, but the fistula was never seen. Endoscopic biopsy of the area was not helpful in establishing either the presence or the nature of the fistula as histological examination of the specimen showed non-specific inflammation in all cases.

Results

Twenty-three patients underwent laparotomy after preliminary bowel preparation. One patient refused operation. A resection and primary anastomosis were performed in all 23 patients. In 12 patients, in whom there was evidence of sepsis, a covering transverse loop colostomy was fashioned. The whole of the sigmoid colon was removed and the anastomosis was made between the descending colon and the rectum; this involved mobilization of the splenic flexure in most cases. Part of the dome of the bladder had to be removed to achieve mobilization of the mass in six patients but in the others the colon was simply 'pinched off' the bladder. The bladder defect was closed with catgut and was covered with omentum.

There were no postoperative deaths. Complications were encountered in five patients; a pulmonary embolus in one, small bowel fistula in one and wound infection in three. The small bowel fistula arose from ileum which was dissected off a malignant sigmoid mass. All the patients were followed up for at least 18 months. One patient died from myocardial infarction 2 years after surgery and one died of locally recurrent carcinoma 3 years after resection.

Histological examination of the excised colon revealed diverticular disease in 16, carcinoma of the large bowel in 6 and Crohn's disease of the colon in 2.

Discussion

Patients with colovesical fistula typically present with symptoms of lower urinary tract infection. Pneumaturia, when present, is usually suggestive of a fistula but occurred in less than half the cases in this series. Therefore, a diagnosis of colovesical fistula should be considered in any patient presenting with intractable proven urinary tract infections. Otherwise the diagnosis may be unnecessarily delayed, particularly in women in whom urinary infections are common. Our experience confirms that of others[1,2] that the condition is more common in men. It has been suggested that the uterus prevents the sigmoid colon and the bladder coming in contact with each other and that therefore colovesical fistulae are less common in women who have not had a hysterectomy[3]. However, no woman in this series had had a hysterectomy.

Physical examination revealed a mass in the left iliac fossa in half of the patients and examination under anaesthetic increases the number of patients in whom a mass can be palpated. We agree with others that sigmoidoscopy is helpful to confirm or exclude the presence of colonic carcinoma although this investigation was useful in only a few patients in this study. Cystoscopy is more informative as the presence of a typical 'pseudo-tumour' on the posterior wall (in patients who are not catheterized previously) is quite characteristic of a fistula. As Morrison and Addison[2] stated, the fistula is often small and is completely obscured by the surrounding oedema. We cannot agree with Shatila *et al.*[4], who found that cystoscopy is useful in making a pathological diagnosis, as biopsies of the bladder from the site of the fistula usually show only features of inflammation. However, endoscopic biopsies are still essential to exclude the possibility of a bladder tumour or colonic neoplasm invading the bladder.

The most useful investigation to confirm the presence of a fistula and its possible pathological basis was a barium enema. This revealed the fistula in more than half the patients and an underlying carcinoma was suspected in three of the six patients with tumour. These findings are similar to other reports of the use of barium enema in this condition[8,9]. Intravenous urography adds little useful information[7]. In our experience, the clinical features and the results of barium enema, cystoscopy and examination under anaesthetic usually leave little doubt about the presence of colovesical fistula; it is rarely necessary to perform other investigations.

Radical resection of the sigmoid colon with limited removal of the vesical tissue is the treatment of choice. A palliative colostomy is inadequate as the fistula rarely closes afterwards[6]. We have not encountered any of the anastomotic problems experienced by others[2,4], even in patients in whom a covering colostomy was not performed. Therefore, when conditions permit, a primary anastomosis without a colostomy should be undertaken.

Colonic diverticular disease is the single most common cause of fistula in this series and those of others[2,4–6]. Neoplastic disease was successfully predicted in three of our patients; the remainder being found by chance in resected specimens. This group have also done well after surgery, only 1 dying after 3 years due to local recurrence.

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Paper accepted 3 November 1986

Case report

Br. J. Surg. 1987, Vol. 74, May, 363

Inguinal hernia: an unusual cause of dyspepsia

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Inguinal herniae affect 6–12 per cent of the world's population. The contents most frequently found within the sac of an inguinal hernia are omentum and small bowel; less frequent are caecum, urinary bladder, sigmoid colon, appendix, and ureter[1,2].

We present an unusual case of an inguinoscrotal hernia containing most of the stomach which produced dyspeptic symptoms in the patient.

Case report

A 49-year-old man presented complaining of weight loss, intermittent abdominal pain, nausea and vomiting. He also admitted postprandial pain and heaviness in the left scrotum limiting his food intake. On examination the only abnormal findings were of large bilateral inguinoscrotal herniae.

In view of the dyspeptic symptoms a barium meal was undertaken. This revealed that the majority of the stomach lay within the sac of the left inguinal hernia (*Figure 1*).

At operation a huge left inguinal hernia sac containing stomach was found. The contents of the sac were successfully reduced into the abdominal cavity, the sac was resected, and a Bassini type herniorrhapy was performed. Recovery was uneventful and the patient was discharged after 7 days. Three months later all symptoms had resolved and weight loss had been regained.

Discussion

Whilst inguinal herniae are common it is extremely rare for the stomach to be contained in the sac; only 50 cases have been described since 1802[1]. The aetiology of the condition is incompletely understood. It may be that omentum first enters the hernia, dilating its neck, and tethering the stomach to the sac. Partial intermittent obstruction would result if the gastric outlet was obstructed at the neck of the hernia. This would increase intra-abdominal pressure, as well as dilating the sac, further aiding the migration of the stomach[2]. We believe this mechanism to be responsible for this patient's symptoms. Very rarely rupture of the stomach can occur if both cardia and pylorus lie within the sac and are obstructed simultaneously[1,3].

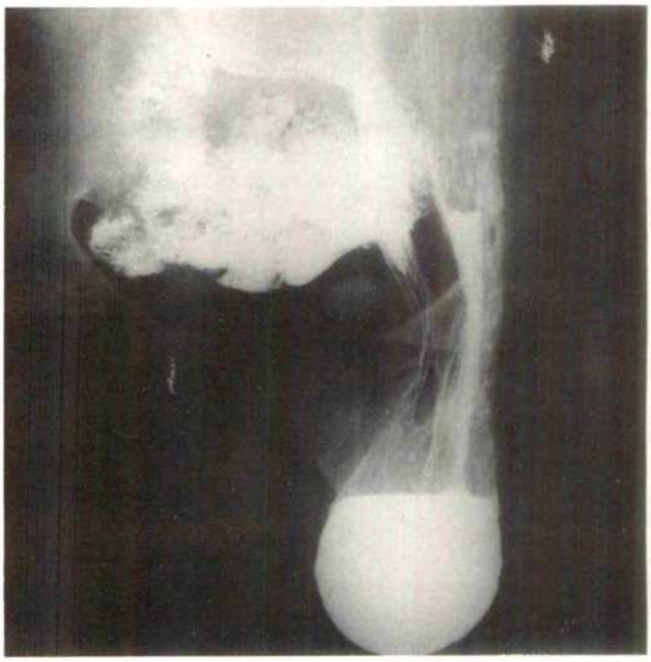

Figure 1 *Barium meal showing the stomach occupying the sac of the left inguinal hernia*

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Paper accepted 14 October 1986

Br. J. Surg. 1987, Vol. 74, May,
364–365

Assessment of ornithine decarboxylase activity in rectal mucosa as a marker for colorectal adenomas and carcinomas

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We have investigated the role of ornithine decarboxylase activity in rectal mucosa as a marker for colorectal neoplasia. Biopsies of normal rectal mucosa were taken from 18 patients with adenomas > 1 cm diameter, 11 with carcinomas and 16 controls. The mean ornithine decarboxylase activity in normal rectal mucosa of adenoma patients, 6·52 nmol CO_2 *released* h^{-1} *(mg cell protein)*$^{-1}$, *was significantly lower than that in controls, 16·8,* P = *0·006. The difference in rectal ornithine decarboxylase activities between cancer patients, 3·58, and controls was also significant,* P = *0·001. These preliminary results suggest that ornithine decarboxylase may be a useful marker in screening for colorectal neoplasia.*

Keywords: Ornithine decarboxylase, colorectal cancer

Most cells in the body contain the polyamines spermidine, spermine and their precursor putrescine[1]. These polyamines are derived from the amino acids L-ornithine and L-methionine and are essential for normal cell growth and differentiation[2].

Several studies have examined their value as potential markers for the presence of colorectal and other malignancies. Raised serum or urinary polyamine levels have been reported in up to 66 per cent of patients with large bowel cancer[3,4]. However, as a general screening test, the measurement of these polyamines in urine or serum appears to be limited by a lack of sufficient specificity and sensitivity[4]. Monitoring their levels might be of more value in assessing tumour-kill in response to anticancer therapy[5].

The synthesis of polyamines requires ornithine decarboxylase. This enzyme is the first and rate limiting factor in the formation of putrescine and the other polyamines[2]. It is normally present in very small amounts in quiescent cells and its activity increases several hundredfold during the early phases of cellular responses to stimuli such as hormones, drugs, tissue regeneration and growth factors[1,2,6,7]. In the experimental animal, tumour promoting agents, including bile acids, have been reported to increase the activity of this enzyme resulting in an increased synthesis of putrescine[8–10].

Mucosal ornithine decarboxylase activity may be a useful marker for potential disease in those at risk of developing familial polyposis[11]. In our study we have investigated whether it could also be applied to the much larger group of non-genetic forms of large bowel cancer[12].

Patients and methods

Three groups of patients were examined.

Adenoma group

We studied 18 patients with colorectal adenomas ⩾ 1 cm diameter identified by double contrast barium enema and sigmoidoscopy: 13 sigmoid polyps, 3 rectal polyps, 1 transverse colon and 1 descending colon. The mean age of the patients was 61 years (range 39–84). Following removal of the adenomas by endoscopic resection, biopsies of macroscopically normal rectal mucosa were obtained from the lower half of the rectum. The approximate distance between the adenomas and biopsy sites ranged from 5 cm in the case of the rectal lesions to 100 cm in that of adenoma in the transverse colon (mean 30 cm). The rectal biopsies and tissue samples from the adenomas were immediately stored in liquid nitrogen for analysis of ornithine decarboxylase activity.

Carcinoma group

We studied 11 patients with adenocarcinomas of the colon or rectum identified by either double contrast barium enema or sigmoidoscopy. All were sampled at the time of operative resection. The tumour distribution was: 4 rectal, 2 sigmoid, 1 left colon, 1 transverse colon and 3 right colon. The mean age of the patients was 66 years (range 42–92). As with the adenoma patients, biopsies of macroscopically normal rectal mucosa were obtained from the lower half of the rectum. The approximate distances between the carcinomas and the rectal biopsy site ranged from 5 to 150 cm in the cases of the ascending colonic tumours (mean 60 cm).

Specimens of tumour were obtained either at the time of diagnostic biopsy or immediately following surgical resection.

Control group

Sixteen patients having treatment for haemorrhoids gave informed consent for low rectal biopsy. The mean age of the controls was 53 years (range 24–82).

Methods

The assay of ornithine decarboxylase activity in the specimens of tissue was carried out according to the method described by Beaven *et al.* in 1978[13]. Activity was expressed in nmol CO_2 released h^{-1} (mg cell protein)$^{-1}$. Statistical analysis for non-parametric data was performed using the Mann–Whitney *U* test.

Results

The mean ornithine decarboxylase activity in rectal mucosa of the control group was 16·8 nmol CO_2 released h^{-1} (mg cell protein)$^{-1}$ (range 3·27–49·2) (*Figure 1*). In the adenoma patients the mean enzyme activity in normal rectal mucosa was 6·52 (range 0–15·9). In normal rectal tissue from the cancer group it was 3·58 (range 0–9·27). In tumour tissue the mean activity was 1·94 for the adenomas (range 0–8·89), and 1·37 for the carcinomas (range 0–4·22). When the activities in macroscopically normal rectal mucosa from the three groups were compared, the mean activity in the adenoma group was significantly lower than in the controls, *P* = 0·006. The mean activity in the rectal mucosa from the carcinoma group was also greatly reduced (*P* = 0·001). While there was a trend for activities in rectal mucosa of the cancer patients to be lower than that in the adenoma group, this did not reach statistical significance. The activity of the enzyme in adenoma tissue and in carcinoma tissue was lower than that of 'normal' rectal tissue from the same patient.

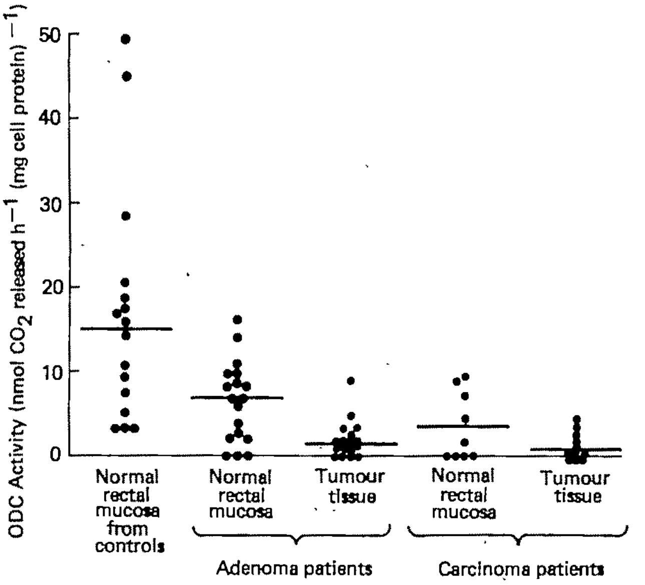

Figure 1 *Ornithine decarboxylase (ODC) activities from rectal mucosal biopsies in normal control subjects compared with patients who have adenomas and carcinomas with specimens taken both from the tumour and the rectal mucosa*

Discussion

We have shown diminished levels of ornithine decarboxylase activity in macroscopically normal rectal mucosa of patients with colorectal tumours. This was unexpected because a study of familial polyposis patients and their relatives had reported increased levels of this enzyme in the familial form of the disease[11].

Rozhin *et al.*[14] reported an increase in tumour patients but the very small numbers studied and the lack of controls precluded statistical analysis of the results. Other studies may help to explain the decreases in activity which we have observed in tumour bearing patients. Experimental studies with animal models have reported a rise in activity following tumour initiation[9,10]. However, it should be noted that such increases were transient and not sustained. In other similar experiments tumour initiation was reported to produce a fall in the activity of the enzyme[15]. How can these conflicting results be reconciled with the reported increases in polyamine levels seen in colorectal cancer? If we examine the biosynthesis of polyamines, it is thought that the activity of ornithine decarboxylase is controlled by putrescine in some manner that is not simply due to product inhibition. The polyamines have been reported to induce the formation of inhibitors to ornithine decarboxylase in cell culture and animal models[4]. It has been suggested that the failure of dimethylhydrazine to produce a rise in activity in mice and yet an increase in putrescine levels may be due to the interconversion of putrescine from spermine and spermidine[15,16], in place of the more usual formation from ornithine under the control of the enzyme. It is reasonable to hypothesize that some initiator resulting in the development of colorectal tumours in man may also produce a transient rise in ornithine decarboxylase activity. With polyamine synthesis set in motion some form of feedback inhibition, as previously described, may reduce the activity to below the normal level as observed in this study.

While there was no significant difference in activities in rectal mucosa of the adenoma and cancer patients, there was a trend suggesting a progressive decrease in activity from controls through adenoma patients to those with carcinomas.

Although the activities in adenoma and carcinoma tissue were still lower than that in rectal mucosa, we cannot be certain of the accuracy of these figures. Adenomas were all removed endoscopically. There was inevitably a few minutes between snaring of the adenomas and removal using grasping instruments. Not only may this period of ischaemia have affected the activity of the enzyme[2], but the heat from the diathermy loop may also have had an important effect. Similarly, the activity of the enzyme in carcinoma tissue may well have been affected by the warm ischaemic time during operative resection.

While there may be some uncertainty over the accuracy of our results from tumour tissue, it should be noted that biopsies of rectal mucosa were all obtained in exactly the same manner from the three groups and frozen immediately so that a valid comparison can be made. Although no direct attempt had been made to match the groups for age and sex, differences in age were small suggesting that this was not a relevant factor in the results.

The observation that ornithine decarboxylase activity in macroscopically normal rectal mucosa up to 150 cm from the tumour was abnormal is potentially important. It could suggest the possibility of some form of field change induced in the colorectum by the tumour promoting agent.

These preliminary results suggest that macroscopically normal rectal mucosa in patients with colorectal tumours is significantly different biochemically from controls. There are potential screening opportunities if these results are confirmed.

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Paper accepted 25 October 1986

Br. J. Surg. 1987, Vol. 74, May,
366–369

Influence of sialomucin at the resection margin on local tumour recurrence and survival of patients with colorectal cancer: a multivariate analysis

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In a multicentre prospective trial 358 patients undergoing curative surgery for colorectal cancer were followed for a median 18·0 months (±7·2 months). The presence or absence of sialomucin in either resection margin was studied using the high iron diamine-alcian blue stain. There was evidence of excess sialomucin at one or other resection margin in 106 patients (29·6 per cent). Apart from sigmoid carcinomas occurring more often in the sialomucin positive group, there were no significant differences in any histological or clinical parameters between groups. Survival analysis for the events 'death', 'local recurrence', and 'all recurrence' was undertaken using the Cox regression model. The best prognostic variables selected in a stepwise fashion for death and all recurrence were 'Dukes' classification', 'sialomucin present' and 'histological differentiation'. The best prognostic variables selected for local recurrence were 'sialomucin present', 'Dukes' classification' and 'histological differentiation'. Sialomucin in a resection margin is an important independent prognostic variable for the development of local tumour recurrence and of subsequent survival for patients with colorectal carcinoma.

Keywords: Colorectal cancer, sialomucin, prognostic variables

Two-thirds of patients who develop colorectal carcinoma will die of their disease within 5 years, including half of those in whom the surgical resection was apparently complete[1]. Tumour 'recurrence' may reflect an inadequate primary operation, occult metastases, implantation of viable cancer cells (e.g. at the anastomosis) or metachronous carcinogenesis[2–5]. Whatever the mechanism, recurrence is usually detected within 2 years of operation[6], but seldom at a sufficiently early stage to permit effective treatment[7].

A reliable method to predict patients who are at special risk of local recurrence is required in whom intensive surveillance and perhaps adjuvant therapy might be appropriate. We have demonstrated abnormal quantities of sialomucin at one or other resection margin in 20 per cent of surgical specimens containing a large bowel cancer[8]. It is unclear whether a change from sulphomucin to sialomucin secretion is a feature of early neoplastic transformation[9] or simply a non-specific response to inflammation[10] or hyperplasia[11]. In a retrospective survey we showed that the presence of a sialomucin predominant pattern of staining at the resection margin was associated with an increased risk of local recurrence[12].

In 1983 we instigated a prospective trial to determine the impact of sialomucin at the resection margin for the prognosis of that particular patient with colorectal carcinoma. The preliminary findings of this trial have already been reported[13]. The final analysis confirms that this histochemical abnormality does indeed indicate a greater susceptibility to local recurrence of the cancer, and subsequent poor survival.

Patients and methods

A prospective study of patients undergoing 'curative' resection of colorectal carcinoma who survived the postoperative period (30 days) was started in January 1983 and involved two teaching hospitals and six district centres (see Acknowledgements). Patient recruitment ended in December 1984. There were 358 patients entered and were available for study. Seven patients were lost to further follow-up after a mean period of 13·6 months observation.

Following resection, biopsies were taken from the proximal and distal resection margins of the specimen and from the tumour and surrounding mucosa. The specimens were processed routinely in paraffin and 4–5 μm histological sections were cut. Sections were stained with haematoxylin and eosin and the high iron diamine-alcian blue stain for detecting sulphomucin and sialomucin[14]. Using this stain normal mucosa mostly stains brown owing to sulphomucin, whilst predominant sialomucin secretion appears as a blue staining reaction.

Three patterns of staining pattern were recognized: purely sulphomucin staining, purely sialomucin staining and a mixed pattern; only the sialomucin predominant pattern was considered abnormal. All the slides were examined independently by two surgeons (P.M.D., N.A.H.) and a pathologist (H.C.R.). Relevant clinical details were noted and all patients were followed either to death or for 1–3 years. Median follow-up was 18·0 months. Patients were recorded as having either local recurrence or no signs of recurrence at this time.

Local tumour recurrence was defined as recurrence at or in the vicinity of the operative site, including the wound but excluding peritoneal deposits or hepatic metastases. Evidence for tumour recurrence was derived from tissue diagnosis, radiography (CT scan, barium enema, ultrasound) or obvious clinical signs. Carcinoembryonic antigen estimations were not routinely employed and have therefore not been analysed. Causes of death were ascertained from the medical records or autopsy (if performed).

The prognostic indices studied were Dukes' staging, histological differentiation, and the presence or absence of sialomucin at one or other resection margin.

Models were constructed for the events: survival (all causes of death), all forms of tumour recurrence and local recurrence only.

Each prognostic variable was analysed by standard survival methods[15] and by multivariate analysis using the Cox regression model[16]. Patients who died within 30 days of radical surgery were excluded from the analysis. Deaths due to other causes were censored observations from the time of death. The prognostic variables were chosen by the formal stepwise regression method using the program

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Table 1 *Site of primary carcinoma in 358 patients undergoing curative resection*

Site	Sialomucin positive *n*	Sialomucin negative *n*	Total *n*
Caecum	9 (8·5)	42 (16·7)	51 (14·2)
Ascending colon	3 (2·8)	21 (8·3)	24 (6·7)
Hepatic flexure	1 (0·9)	6 (2·4)	7 (2·0)
Transverse colon	2 (1·9)	9 (3·6)	11 (3·1)
Splenic flexure	3 (2·8)	6 (2·4)	9 (2·5)
Descending colon	2 (1·9)	13 (5·2)	15 (4·2)
Sigmoid colon	45 (42·5)	66 (26·2)	111 (31·0)
Rectum	41 (38·7)	84 (33·2)	125 (34·9)
Multiple	0 (0)	5 (2·0)	5 (1·4)
Total	106	252	358

Values in parentheses are percentages
$\chi^2=19{\cdot}394$, 8 d.f., $P<0{\cdot}02$

Table 2 *The operations performed in the sialomucin positive and negative groups*

Operation	Sialomucin positive *n*	Sialomucin negative *n*	Total *n*
Right hemicolectomy	14 (13·2)	81 (32·1)	95 (26·5)
Transverse colectomy	0 (0)	3 (1·2)	3 (0·8)
Left hemicolectomy	6 (5·7)	15 (6·0)	21 (5·9)
Sigmoid colectomy	40 (37·7)	62 (24·6)	102 (28·5)
Anterior resection	29 (27·4)	52 (20·6)	81 (22·6)
Abdominoperineal excision	10 (9·4)	32 (12·7)	42 (11·7)
Hartmann's	4 (3·8)	2 (0·8)	6 (1·7)
Total colectomy	3 (2·8)	5 (2·0)	8 (2·2)
Total	106	252	358

Values in parentheses are percentages
$\chi^2=22{\cdot}23$, 7 d.f., $P<0{\cdot}001$

BMDP2L (W. J. Dixon, BMDP Statistical Package, UCLA 1983). The variables were thereby selected in steps until no further effect upon the events could be demonstrated.

Results

There were 189 females (mean age 66·6 years) and 169 males (mean age 64·6 years). The primary sites of tumour and the operations performed are shown in *Tables 1* and *2*.

Sialomucin predominated at the proximal resection margin in 51 cases (18·6 per cent) and at the distal resection margin in 72 cases (22·4 per cent). There was evidence of excessive sialomucin secretion in one or other resection margin in 106 patients (29·6 per cent). The ileum constituted the proximal resection margin in 84 cases and the anal margin the distal margin in 37 cases and have been excluded from the calculations. Sialomucin was seen significantly more often in patients with sigmoid carcinoma.

There was no significant association between Dukes' classification of the primary tumour or histological differentiation on the one hand and the presence or absence of sialomucin on the other hand (*Tables 3* and *4*). Similarly, no association was observed with age, sex or distance of the resection margins from the primary.

Within the 18 month period of follow-up 101 patients (28 per cent) developed recurrence (*Table 5*). Recurrence was demonstrated locally in 62 cases, 32 of which occurred in the sialomucin positive group. Six patients in the sialomucin positive group had anastomotic recurrence compared with three in the sialomucin negative group. Local and distant recurrent disease were diagnosed by biopsy in 36 cases, ultrasound in 20 cases and CT scan of pelvis in 11. The remaining 34 patients had definite clinical signs. Because of the difficulties implicit in a multicentre study only six patients had a necropsy.

To date 76 patients have died from their cancer, 34 (33 per cent) in the sialomucin positive group and 42 (16·8 per cent) in the sulphomucin group. The mean time to recurrence in both groups was 11·1 months (sialomucin positive) and 12·4 months (sialomucin negative, median 11 months). Twenty patients have undergone further laparotomy. Six patients have had recurrent tumour excised whilst a further six patients have developed metachronous tumour (five of which occurred in the sialomucin negative group).

The relationship between tumour recurrence and site of the primary in both the sialomucin positive and negative groups is shown in *Table 6*. The percentage recurrence rate at each site ranged from 8 to 42 per cent. More recurrences occurred in the left colon although a significant difference between groups was not seen. Life table analysis of survival by site of the primary tumour was not significantly different (Lee–Desu statistic = 5·985, $P<0{\cdot}64$). Tumour recurrence was seen in 4 patients with Dukes' A carcinoma (4 per cent), 43 patients (42·6 per cent) with Dukes' B and 54 (53·5 per cent) with Dukes' C classification.

The survival curve of the prognostic variable, presence or absence of sialomucin in a resection margin is shown in *Figure 1*. Using the Cox regression model for all prognosis variables, the best prognostic indicators for the event 'survival' were: Dukes' classification, sialomucin present, and histological differentiation. The best predictive variables for the event 'all types of recurrence' were the same. The best predictive variables for the event 'local recurrence' were: sialomucin present, Dukes' classification, and histological differentiation (*Table 7*).

Table 3 *Dukes' classification of the primary lesions in the sialomucin positive and negative groups*

Dukes' classification	Sialomucin positive *n*	Sialomucin negative *n*	Total *n*
A	7 (6·6)	35 (13·9)	42 (11·7)
B	68 (64·2)	138 (54·8)	206 (57·5)
C	31 (29·2)	79 (31·3)	110 (30·7)
Total	106	252	358

Values in parentheses are percentages
$\chi^2=4{\cdot}62$, 2 d.f., n.s.

Table 4 *Histological classification of the primary lesions in the sialomucin positive and negative groups*

Differentiation	Sialomucin positive *n*	Sialomucin negative *n*	Total *n*
Good	16 (15·1)	39 (15·5)	55 (15·4)
Moderate	75 (70·8)	184 (73·0)	259 (72·3)
Poor	10 (9·4)	23 (9·1)	33 (9·2)
Variable	5 (4·7)	6 (2·4)	11 (3·1)
Total	106	252	358

Values in parentheses are percentages
$\chi^2=1{\cdot}392$, 3 d.f., n.s.

Table 5 *The sialomucin status of the resection margin and tumour recurrence*

Type of recurrence	Sialomucin positive *n*	Sialomucin negative *n*
Locoregional alone	11 (10·8)	13 (5·1)
Locoregional and metastases	21 (20·8)	17 (6·7)
Metastases alone	8 (7·9)	25 (9·9)
Total	40	55

Values in parentheses are percentages
$\chi^2=7{\cdot}155$, 2 d.f., $P<0{\cdot}02$. Excludes metachronous tumours ($n=6$)

Table 6 *Details of tumour recurrence in 101 patients in relation to the site of the primary*

Site	Recurrences n (%)	Percentage of total	Metachronous tumour	Sialomucin positive n (%)	Sialomucin negative n (%)
Caecum	16 (15·8)	31·4	1	4 (25)	11 (68)
Ascending colon	2 (2)	8·3	0	0 (0)	2 (100)
Hepatic flexure	3 (3)	42·8	1	0 (0)	2 (66)
Transverse colon	4 (4)	36·3	0	0 (0)	4 (100)
Splenic flexure	1 (1)	9·1	0	1 (100)	0 (0)
Descending colon	5 (5)	33·3	0	1 (20)	4 (80)
Sigmoid colon	24 (23·8)	21·6	2	12 (50)	10 (41)
Rectum	45 (44)	36	2	21 (46)	22 (48·8)
Multiple	1 (1)	16·6	0	1 (100)	0 (0)
Total	101		6	40	55

Table 7 *Stepwise regression analysis (Cox models) for the events, 'survival', 'all recurrence', and 'local recurrence'*

Event	Step no.	Variable entered	d.f.	Improvement χ^2	P
Survival	1	Duke's classification	1	23·660	0·0001
	2	Sialomucin pattern	2	11·310	0·001
	3	Histological differentiation	3	5·97	0·015
All recurrence	1	Dukes' classification	1	31·684	0·0001
	2	Sialomucin pattern	2	10·14	0·001
	3	Histological differentiation	3	3·905	0·048
Local recurrence	1	Siaolomucin pattern	1	16·828	0·0001
	2	Dukes' classification	2	10·217	0·001
	3	Histological differentiation	3	4·268	0·039

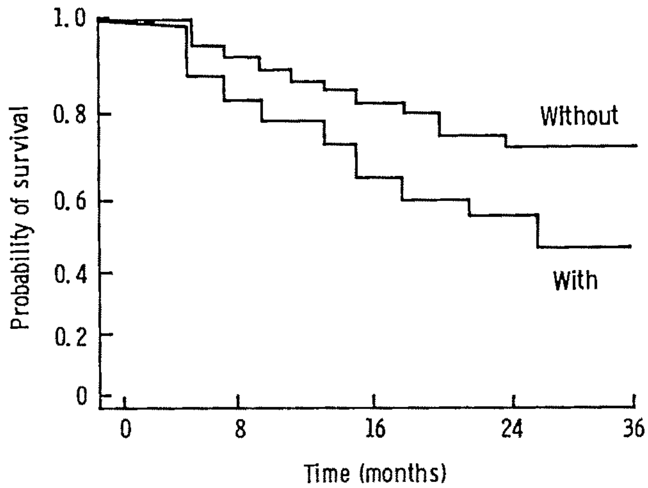

Figure 1 *Life tables of survival for the prognostic variable sialomucin present or absent in the resection margin* ($P < 0{\cdot}0004$, *Lee–Desu statistic 12·323, 1 d.f.*)

Discussion

This study has demonstrated a correlation between the appearance of sialomucin at either resection margin and the development of local recurrence of colorectal carcinoma and subsequent death within the 18 months of median follow-up. This appears to confirm the retrospective study[12] and demonstrates sialomucin to be an independent prognostic variable. The implication of these data could clearly affect current surgical practice. Patients shown to be at risk of tumour recurrence might be candidates for adjuvant therapy from operation. Alternatively, if a staining technique could be developed for intraoperative use to screen for abnormal mucus change, further colonic resection might be appropriate until a normal staining pattern was found in the remaining intestine.

The interpretation of these findings requires caution. The low rate of autopsy precludes the exact incidence of recurrent tumour, particularly of the right side of the colon, the incidence of which is almost certainly higher. Similarly the influence of the ileum at right sided restorative procedures is unknown, perhaps reducing the incidence of recurrence seen at this site. Nevertheless the Cox models identified sialomucin as the best independent prognostic variable for local tumour recurrence having accounted for all the other prognostic variable modifying influences.

It is doubtful that the changes observed are pre-malignant. Nevertheless these changes extend to the resection margin in one fifth of cases[8], leaving abnormal colonic tissue at an anastomosis, with local tumour recurrence as a sequel of this event. Sialomucin does not, however, appear to be related to the development of metachronous tumour.

Sialomucin cannot be the sole mechanism of local tumour recurrence, and although a strong association has been demonstrated, many tumour recurrences must occur outside the bowel lumen to secondarily invade the bowel at the weakest point (i.e. the anastomosis). The higher incidence of anastomotic recurrence, however, lends support to the contention that sialomucin may represent premalignancy.

The high iron-diamine alcian blue stain is a simple and inexpensive staining technique which appears to identify patients at risk of tumour recurrence more accurately than other established techniques. It offers the prospect of treating or avoiding recurrent carcinoma at a much earlier stage and thus the chance of improved survival.

Further investigation is needed of the relationship between the histochemical properties of colonic mucous and the process of malignant transformation.

Acknowledgements

We wish to thank Dr K. D. MacRae, Reader in Medical Statistics, Charing Cross and Westminster Medical School for direction and help with the statistics. Miss A. M. Curran for typing the manuscript and Mrs R. Samosir for assistance with computing. The Cancer Research Campaign partly funded the work.

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Paper accepted 16 November 1986

Br. J. Surg. 1987, Vol. 74, May,
370–372

Outcome of colorectal cancer

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The outcome of 454 patients who presented with colorectal carcinoma during a 16 year period is reviewed: 54 per cent were males, 58 per cent were aged more than 60 and 10 per cent had an emergency admission, 42 per cent of tumours occurred in the rectum. A curative resection was possible in 68 per cent. Postoperative mortality was 7 per cent. The overall crude 5-year survival was 41 per cent. The mortality from local recurrence was significantly higher in rectal (11·7 per cent) than in colonic cancer (8·8 per cent; $P<0{\cdot}01$*). The rate of recurrence and metastases was higher in patients with low rectal cancer than in patients with cancer of the middle and the upper rectum (*$P<0{\cdot}01$*). Distant metastases were the cause of death in 94 per cent of the patients who had a Miles' operation for cancer of the middle rectum, whereas local recurrence was responsible for late mortality in 80 per cent of patients who underwent an anterior resection. No difference in 5-year survival was found in the restorative and in the excisional group.*

Keywords: Colorectal cancer, survival, recurrence, metastasis

Every year about 25 000 new patients are hospitalized in Italy for colorectal cancer. According to the Italian Institute of Statistics 10975 patients died of large bowel cancer in 1980 (6504 colonic, 4471 rectal cancer; 5687 males, 5288 females). Although a radical operation is usually possible in two-thirds of the patients, only one-third has the chance of permanent cure, owing to occult metastases at the time of surgery. The 5-year survival rate varies between 30 and 40 per cent, but it increases to 55 per cent in specialized units. The aim of this study is to analyse the outcome of 454 malignant large bowel tumours surgically treated in a department of general surgery in Italy.

Patients and methods

A total of 454 patients with histologically proven colorectal cancer, admitted to the Istituto di Clinica Chirurgica of the Catholic University of Rome between January 1967 and December 1980, forms the basis of this study.

No tumour was classified as carcinoma unless there was definite invasion of malignant cells through the muscularis mucosae. Clinical records were reviewed, age and sex were recorded. Operative details and pathological findings were analysed, and all patients were allocated to one of the following stages:stage A, confined to the bowel wall; stage B, penetration of the bowel wall by the tumour; stage C, involvement of regional lymph nodes; stage D, involvement of distant peritoneum or remote metastases. Location of the neoplasm, mode of presentation, indication for emergency, type of operation carried out, and percentage of radical interventions were also recorded. Forty-two per cent of the neoplasms were located in the rectum, the lower edge of the lesion being located no more than 15 cm from the anal verge at sigmoidoscopy or level with or below the sacral promontory at laparotomy.

We defined the lower rectum as being from 0 to 7 cm from the anal verge; middle rectum, 7–11 cm; upper rectum, 11–15 cm, including the rectosigmoid junction. Radical procedures were defined as operations in which all known tumour was excised, with no evidence of residual disease. Postoperative complications were divided into general and local. Postoperative deaths, that is occurring up to 30 days after the operation, were recorded and related to the site of the tumour and the pathological staging. Follow-up data were available in 94 per cent (428 patients). Twenty-six patients, 13 with a rectal cancer, 13 with a colonic cancer, were lost to follow-up. They were included in the analysis of all the clinical data, except for analysis of local or distant recurrence and subsequent survival. Patients who had multiple tumours or who did not have surgery were excluded from the study. Mechanical preparation was used before elective surgery. Prophylactic antibiotics were given systematically just before anaesthesia and 36 h postoperatively in all cases. Most of the operations were performed by senior surgeons.

The χ^2 test was used for statistical analysis.

Results

Age, sex, type of surgery and pathological staging

Age distribution of the patients and site of the tumour are shown in *Tables 1* and *2*. More than half were aged over 60 years. The male:female ratio was 1·14:1. Most of the patients (90·3 per cent) underwent elective operations (*Table 3*). The emergency operations were due to perforation (9 patients) and intestinal obstruction (35 patients). The operations performed are listed in *Table 4*. Staging classified only 13 (2·9 per cent) patients as Group A; 148 (32·6 per cent) as Group B; 157 (34·5 per cent) as Group C; 136 (30 per cent) as Group D.

Table 1 *Age distribution of the patients*

Age (years)	No.	Percentage
20–40	20	5
40–60	169	37
60–80	265	58
Total	454	100

Table 2 *Site of the tumour*

Site	No.	Percentage
Rectum	191	42
Colon	263	58
Total	454	100

Table 3 *Elective and emergency, radical and palliative surgery*

Surgery	No.	Percentage
Elective	410	90
Emergency	44	10
Total	454	100
Radical	307	68
Palliative	147	32
Total	454	100

Postoperative complications and mortality

Clinically relevant postoperative complications were observed in 165 patients (36·3 per cent). They were more commonly local rather than systemic (24·4 *versus* 11·9 per cent). Overall postoperative mortality was 7 per cent (32 cases), equally distributed between colon and rectal cancer (19 and 13 patients, respectively).

Survival and recurrence

The overall crude 5-year survival was 41 per cent. Ten per cent of the patients died of local recurrence, 45 per cent died of metastases, the remaining 4 per cent died of causes unrelated to the cancer. Of the 191 patients with rectal cancer 29 were not considered in the long-term study (13 lost at follow-up, 13 died of postoperative complications, 3 died of other causes); 19 (11·7 per cent) of the remaining 162 died of local recurrence. Twenty patients (8·8 per cent) of the 227 who had colonic cancer died of recurrence.

The mortality of local recurrence was significantly higher in rectal than in colonic cancer ($P < 0{\cdot}01$).

Rectal cancer

Most of the patients who died of distant metastases (30 per cent) or both local and distant recurrence (11 per cent) due to rectal cancer had lymph node involvement at the time of surgery (*Table 5*). Most of those with distant metastases at the time of operation died within 1 year.

Local recurrence was rarely (3 per cent) a cause of death more than 3 years after surgery.

Cancer of the lower rectum showed a higher incidence of both local recurrence and distant metastases when compared with cancer of the middle and upper rectum ($P < 0{\cdot}01$, see *Table 6*).

Twenty-one out of 47 patients who were operated on for cancer of the middle rectum died within 5 years of surgery. Distant metastases were the main cause of death and mainly occurred after Miles' operation (*Table 7*).

Discussion

Most patients were aged over 60 years. There was a predominance of males and nearly half the tumours were located in the rectum. The same findings are reported by others[1–3]. Prognosis and mode of presentation may be influenced by age. Patients over 70 show a poor 5-year survival[4] and a high emergency operation rate leading to a higher mortality[3]. On the other hand a low survival rate has also been reported in patients under 40, due to the high malignancy of their tumours[5]. According to Umpleby *et al.*[1], survival after curative resection was not affected by age. Radical surgery was achieved in 68 per cent of our patients. The figure agrees with other reports[1,6–8], but is lower than the one reported by specialized centres[8]. Between 30 and 60 per cent of all rectal carcinomas are now treated by sphincter-saving procedures compared with about 10–20 per cent in the 1950s[9–11].

A trend towards more sphincter-saving procedures is observed when comparing the present study to a previous one carried out in our unit. The percentage of abdomino-perineal excision and anterior resection were 49 and 16 per cent of 161 colorectal tumours operated on up to 1975[12]. Therefore the excisional:restorative operations ratio decreased from 3:1 to 1·5:1 in a 5-year period. An overall postoperative mortality rate of 7 per cent was observed in our series, lower than the one reported from general hospitals with a large number of emergencies[2], but higher than observed in specialized centres[9]. The site of the tumour did not influence the mortality rate. The overall crude 5-year survival was 41 per cent, better than in a previous report from the same unit[12]. Other authors from departments of general surgery report a survival of 32 per cent[1–2], whereas the prognosis seems again to be better in centres devoted to colorectal surgery[9].

Neoplastic lymph node involvement at the time of surgery leads to a worse prognosis, in terms of both local recurrence and distant metastases. The type of procedure chosen for cancer of the mid-rectum, whether restorative or excisional, did not seem to influence 5-year survival in our series, whereas a better prognosis after Miles' operation has been reported by others[13].

The difference in survival probably reflects selection criteria rather than differences in therapy. It is unlikely, in fact, that the choice of local operation may affect the occurrence of occult distant metastases. The results of a recent study suggest that for patients with rectal cancer radical excision with sphincter preservation using the circular stapler has a mortality, morbidity and risk of local recurrence comparable with radical excision with a permanent colostomy[14]. However, in our study most of the deaths in the restorative group were due to local recurrence and caused by distant metastases in the excisional cases. Both an incomplete clearance of tissue distally and laterally to the tumour and an implantation of neoplastic cells are more likely to occur after low anterior resection. Perhaps this could explain the higher number of local recurrence we observed after restorative surgery.

The question arises whether surgeons in Italy should not be attempting to perform an increasing proportion of restorative

Table 4 *Type of operations performed*

Operation	No.	Percentage
Miles'	127	28
Anterior resection	86	19
Right hemicolectomy	72	16
Diverting colostomy	59	13
Left hemicolectomy	41	9
Laparotomy	32	7
Hartmann's	27	6
Local excision	10	2
Total	454	100

Table 6 *Cancer of lower, middle and upper rectum. Distribution of 71 recurrences and 67 metastases according to the site of the original tumour*

Site	Recurrences	Metastases
Lower rectum	51	45
Middle rectum	14	15
Upper rectum	6	7

Table 5 *Mortality for recurrences and metastases in rectal cancer according to different pathological staging*

		Less than 3 years after surgery		More than 3 years after surgery	
Stage	No.	R (%)	M (%)	R (%)	M (%)
A	6	0	0	0	0
B	66	2 (3)	1 (1)	2 (3)	4 (6)
C	63	11 (17)	22 (35)	0	4 (6)
D	27	4 (15)	22 (81)	0	0

R, no. of patients dead of local recurrence; M, no. of patients dead of distant metastases

Table 7 *Mortality for recurrences and metastases after curative excisional and restorative operations for cancer of the middle rectum*

Operation	No.	Percentage of corrected 5-year survivors	Died within 5 years: of recurrences	of metastases	Total
Miles'	36	55·5	1	15	16
Anterior resection	11	54·5	4	1	5
Total	47	55·0	5	16	21

operations for rectal cancer. A sphincter-saving procedure may be more rewarding both for the surgeon and for the patient, provided that the risk of local recurrence is minimized by a careful selection of the cases; the size of the tumour and its histological grading should be taken into account. Moreover the anal sphincter function should be evaluated before surgery to exclude the subjects with sphincteric disorders and prevent postoperative incontinence after very low anterior resection and coloanal anastomosis. An anastomotic recurrence after anterior resection can be detected early if followed up in a specialized clinic by faecal occult blood testing, contrast studies and endoscopy. Such presymptomatic diagnosis might lead to a benefit in survival.

Acknowledgements

The authors are indebted to Professor G. C. Castiglioni and Dr I. Lavery who kindly revised the manuscript.

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Paper accepted 25 November 1986

Br. J. Surg. 1987, Vol. 74, May,
373–376

Anorectal myectomy for outlet obstruction

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Anorectal myectomy has been evaluated in 29 patients with chronic constipation associated with outlet obstruction. Eight patients had histological evidence of aganglionosis. No patient was able to defaecate spontaneously more than once a week before operation. Eighteen (62 per cent) patients were able to defaecate spontaneously more than 3 times a week after operation (good results) whereas 11 patients were not. There was a significant fall in maximum resting anal pressure after operation in the patients having a good result (102·7 ± 16·7 to 79·5 ± 27·8 cm H_2O) whereas there was no significant fall in those having a poor result (118·4 ± 25·0 to 108·8 ± 28·5 cm H_2O). The operation had no influence on squeeze pressures, length of the high pressure zone, rectal sensation or the anorectal angle. These results seem to indicate that the therapeutic effect of anorectal myectomy is merely due to reduced resting anal canal pressures.

Keywords: Chronic constipation, anorectal myectomy, maximum resting anal pressure

Idiopathic chronic constipation can be classified into two broad functional groups: 'outlet obstruction' and 'colonic inertia'[1]. Outlet obstruction is characterized by a failure to defaecate because the pelvic floor does not relax during attempted defaecation. This condition can be identified by electromyographic evidence of increased activity of the puborectalis during defaecation, or by proctogram evidence of failure to expel rectal contents during defaecation[2,3]. Colonic inertia is a condition where constipation is due to slow transit in the colon and can be assessed by radio-opaque transit markers and colonic motility studies[3,4]. Outlet obstruction and colonic inertia are sometimes present in the same patients with constipation[5,6].

Anorectal myectomy is probably appropriate only for patients with outlet obstruction and encouraging results have been reported in children with this disorder[6–8]. A 1 cm wide strip of the internal sphincter and rectal smooth muscle measuring 10 cm in length is excised after developing the submucosal and intersphincteric plane from the posterior wall of the anorectum. The procedure was designed initially merely as a method of excluding short segment Hirschsprung's disease histologically. We report the results of this operation and speculate on the reason for the therapeutic effect of anorectal myectomy in outlet obstruction.

Patients and methods

Twenty-nine patients with chronic constipation were referred to The General Hospital Birmingham for investigation. All had an anorectal myectomy between June 1984 and April 1986 to exclude Hirschsprung's disease. All of the patients had two of three features suggesting a diagnosis of 'outlet syndrome' (failure to expel a balloon containing $80\,cm^3$ air from the rectum, increased electrical activity in the puborectalis on attempted defaecation or failure to evacuate contrast during proctography). Five patients were male and twenty-four were female. The mean age was 35·5 years (range 15–72). Natural bowel habit (no laxatives, bowel stimulants or suppositories) was compared before and 4 months after operation (*Figure 1*). No patient was able to defaecate spontaneously more than once a week before operation (mean 3·3 ± 0·7/month), whereas the mean bowel habit after operation was 21·8 times a month: hence at least every other day. We reviewed our results by classifying patients into two groups: a 'good results' group in which patients were able to defaecate spontaneously more than 3 times a week after operation and the remainder with 'poor results' who were unable to defaecate spontaneously more than 3 times a week. Manometric examination and proctograms were performed where possible before and 4 months after operation. Colonic transit and electromyography were also assessed before operation[5].

Anal canal pressures were measured in the left lateral position after rectal examination using a closed water-filled balloon probe attached to a transducer and pen recorder as previously described[9,10]. Measurement of resting and squeeze anal pressures were performed at 1 cm intervals 1–5 cm from the anal verge. The maximum resting pressure was taken as the highest resting pressure at the five recording sites. The maximum squeeze pressure was the highest pressure recorded after repeated voluntary contractions at each recording site. With a soft latex balloon positioned in the rectal ampulla just above the levator ani, response of the resting anal pressure to distension with incremental aliquots of 50 ml of air to a volume of 400 ml, was monitored. Reduction of more than 10 per cent of the resting pressure was recorded as an intact recto-anal inhibitory reflex.

Rectal sensation was assessed using the same rectal balloon. Three parameters of sensation were recorded according to the criteria of Farthing and Lennard-Jones[11]: threshold volume, volume associated with constant rectal sensation and volume below 400 ml at which pain become intolerable (maximum tolerable volume). In many of the constipated patients a volume of 400 ml caused no apparent discomfort, but further volumes were not introduced for fear of bursting the balloon.

Colonic transit was assessed while the patient was eating a normal diet and taking no laxatives. Fifty radio-opaque pellets were taken by mouth and a plain X-ray of the abdomen was obtained 5 days later. Transit was recorded as the percentage of radio-opaque markers passed within 5 days.

Electromyography of the pelvic floor was recorded using a concentric needle electrode. Single fibre electromyography was not used in this study. Electrical activity was recorded at rest, during maximal pelvic floor contraction and after attempted defaecation. Electrical activity in normal subjects was always reduced during attempted defaecation. If there was more electrical activity during defaecation than at rest, this phenomena was considered to be abnormal.

Anorectal angles were measured from radiographs taken during defaecating proctograms with the patient seated on a lavatory pan using Baritop mixed with cellulose to achieve a consistency similar to that of faeces. Angles between the anal canal and the posterior wall of the rectum were assessed using an image intensifier linked to a video screen at rest, during maximal pelvic floor contraction and during attempted defaecation.

Statistical analysis of the numerical data was compared using the Mann–Whitney *U* test.

Operative procedure

Anorectal myectomy is performed under general anaesthesia with the patient in the lithotomy position. A Park's anal retractor was inserted

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Based on a presentation to the British Society of Gastroenterology, Cardiff, UK, September 1986

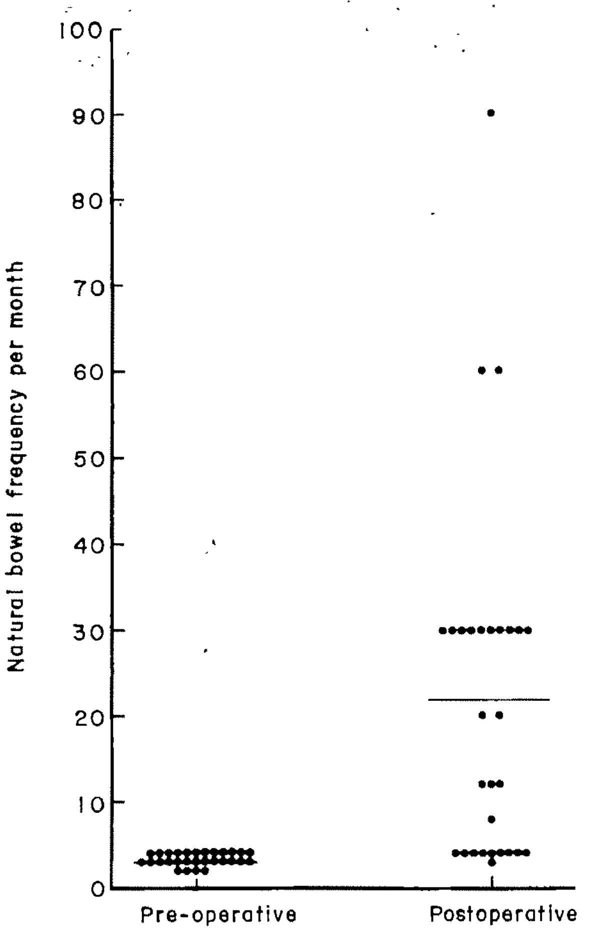

Figure 1 *Natural bowel habits before and 4 months after operation. The horizontal line shows the mean postoperative value of 21·8 times per month,* $P<0.005$

Table 1 *Results of operation*

	Total	Good results	Poor results
No. (%)	29	18 (62)	11 (38)
Mean age (years)	35·5	35·6	35·4
Sex			
Male	5	5	0
Female	24	13	11
Mean natural bowel habits (per month)			
Pre-operative	3·3±0·7	3·1±0·8	3·5±0·5
Postoperative	21·8±20·6*	32·6±19·5*	4·3±1·3
Hirschsprung's disease	8	8	0

* $P<0.005$ compared with pre-operative value

(handles at 12 o'clock). After infiltration of the submucosal and intersphincteric plane with adrenaline in saline (1:300 000) a transverse incision is made approximately 1 cm above the dentate line posteriorly. The mucosa is separated from the internal sphincter and the rectal smooth muscle by scissor dissection and retracted upwards using the third blade of the Park's retractor. In order to remove the entire length of the internal sphincter, the mucosa below the dentate line must be dissected off the smooth muscle until the lower limit of the muscle is reached. After further infiltration in the inter sphincteric plane the internal sphincter and rectal smooth muscle is then dissected from the posterior fibres of the external sphincter and puborectalis. A 1 cm width of smooth muscle is then excised over a length of 10 cm after marking the distal margin with a suture. After haemostasis the mucosal incision is closed using a continuous catgut suture. A sponge is left inside the anal canal for 4 h to provide some tamponade. The excised specimen of smooth muscle and internal sphincter is subsequently examined histologically.

Results

Eighteen patients (62 per cent) achieved a good result (*Table 1*). In the patients having a good result, the mean frequency of bowel habit was improved from 3·1±0·8 to 32·6±19·5 bowel movements per month ($P<0.005$). In the poor results group, the mean bowel frequency was not changed after operation (3·5±0·5 to 4·3±1·3 bowel movements per month). There was no significant difference in mean age between the two groups. All male patients had a good result. Eight patients (28 per cent) were found to have Hirschsprung's disease and all achieved good results following anorectal myectomy.

Overall there was a significant fall in maximum resting anal pressure after operation from 107·6±20·2 to 88·6±30·5 cm H_2O ($P<0.05$). In the group who had a good result, resting anal pressure decreased from 102·7±16·7 to 79·5±27·8 cm H_2O ($P<0.05$). However, no significant change in pressure was found in the poor results group (118·4±25·0 to 108·8±28·5 cm H_2O). Maximum squeeze pressure did not change significantly after operation overall or in either of the subgroups (*Table 2*). The pre-operative maximum resting anal pressure and maximum squeeze pressure were greater in the poor results group but these differences were not statistically significant.

Overall, the threshold volume, constant sensation and maximum tolerable volume did not change significantly after operation or in either subgroup (*Table 3*). The recto-anal inhibitory reflex was evaluated in 26 patients before operation. The reflex was present in 17 patients (65 per cent) of whom 10 of 16 were in the good results group and 7 of 10 in the poor results group. Absence of the recto-anal inhibitory reflex was not diagnostic of Hirschsprung's disease since the reflex was present in 4 of 7 with Hirschsprung's disease and absent in 6 of 19 with normal histology. Increased electrical activity of the puborectalis muscle during attempted defaecation was detected in 6 of 16 patients (38 per cent) overall. Four of them were in the good results group and two in the group having a poor result. The mean colonic transit of the poor results group was greater than the remainder but the difference was not statistically significant (*Table 4*).

The mean anorectal angles during rest, maximum pelvic floor contraction and during attempted defaecation were 86·9±16·8, 82·3±14·3 and 114·1±13·0 before operation. In each position there was no overall difference after operation or in either subgroups (*Figure 2*).

Table 2 *Anal canal pressures*

	All cases ($n=16$)		Good results ($n=11$)		Poor results ($n=5$)	
	Pre-operative	Postoperative	Pre-operative	Postoperative	Pre-operative	Postoperative
Maximum resting anal pressure (cm H_2O)	107·6±20·2	88·6±30·5*	102·7±16·7	79·5±27·8*	118·4±25·0	108·8±28·5
Maximum squeeze pressure (cm H_2O)	233·0±55·7	212·5±84·8	227·5±41·7	201·3±64·5	245·2±83·8	237·2±124·4

* $P<0.05$ compared with pre-operative value

Table 3 *Rectal sensation*

	All cases ($n=15$)		Good results ($n=11$)		Poor results ($n=4$)	
	Pre-operative	Postoperative	Pre-operative	Postoperative	Pre-operative	Postoperative
Threshold volume (ml)	63·3±29·7	66·7±52·3	63·6±32·3	72·7±60·7	62·5±25·0	50·0±0
Constant sensation (ml)	203·3±121·7	183·3±124·9	213·6±116·4	190·9±117·9	175·0±150·0	162·5±160·1
Maximum tolerable volume (ml)	360·0±47·1	350·0±80·2	368·2±40·5	354·5±78·9	337·5±62·9	337·5±94·6

Table 4 *Recto-anal inhibitory reflex (RAIR), electromyography (EMG) and colonic transit before operation*

	All cases	Good results	Poor results
RAIR			
Present	17	10	7
Absent	9	6	3
EMG			
Increased activity on defaecation	6	4	2
Inhibition on defaecation	10	7	3
Mean colonic transit (percentage passed per 5 days)	37·6 ($n=17$)	35·6 ($n=12$)	42·2 ($n=5$)

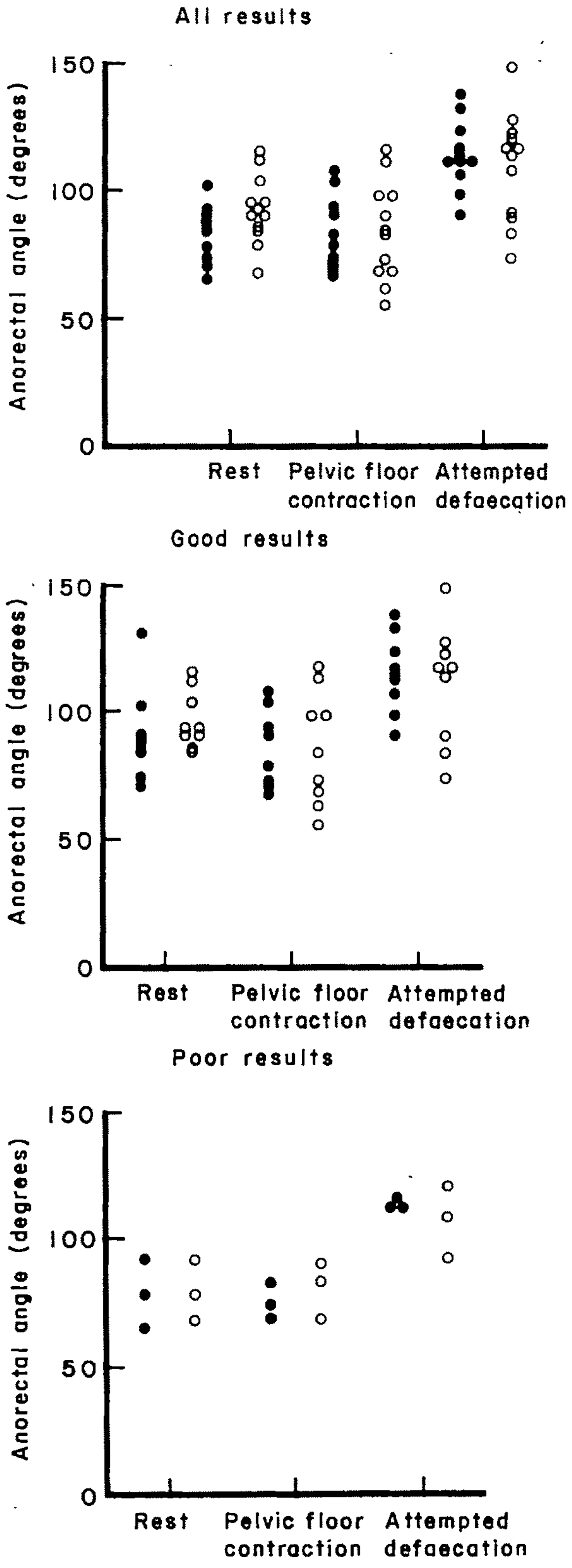

Figure 2 *Anorectal angle before and after operation in each position.* ●, *Pre-operative;* ○, *postoperative. There were no significant differences between the values*

Discussion

We have performed anorectal myectomy in patients with constipation and outlet obstruction mainly to exclude Hirschsprung's disease. Eight of twenty-nine patients (28 per cent) in this study were found to have aganglionosis affecting a variable length of the specimen and in all of these patients symptoms were improved by anorectal myectomy. Encouraging results have also been reported in children with Hirschsprung's disease having anorectal myectomy[6–8]. Nissan *et al.* performed 11 cases of anorectal myectomy for children and symptoms disappeared in most patients following operation[6]. Thomas *et al.* also reported the results of 11 cases of anorectal myectomy and 8 were substantially improved following operation[7]. On the other hand, Martelli *et al.* reported 62 adult patients who had an anorectal myectomy[1], only 14 patients (23 per cent) had aganglionosis and the functional results following operation were generally disappointing.

We found that 62 per cent of patients were initially improved by operation and more prolonged follow-up indicates that these early results are uniformly maintained. Furthermore, maximum resting anal pressures were significantly decreased after operation particularly in patients having a good result. Internal anal sphincter myectomy for anal fissure also produced a 50 per cent fall in sphincter pressure[12]. Our operation involving a 10 cm long myectomy of the internal anal sphincter and rectal smooth muscle was clearly associated with a significant reduction in maximum resting anal pressure. However, it is not certain why the reduction of maximum resting anal pressure is responsible for improving symptons. Early results from this unit also suggest that the increased anal pressures which occur during attempted defaecation are also reduced by anorectal myectomy. Anal dilatation results in a sustained reduction in maximum resting anal pressure[13,14]. Therefore, if the reduction of maximum resting anal pressure is the only reason for the therapeutic effect of anorectal myectomy it might be assumed that these patients could be treated by anal dilatation. Indeed Taylor and others[15] found that anal dilatation did improve symptoms in some patients with obstructed defaecation. We are currently comparing controlled dilatation with anorectal myectomy for outlet obstruction.

Martelli and others[1] suggested that absence of a recto-anal inhibitory reflex before surgery may have prognostic implications, but in our study we found it impossible to predict the results of operation from the absence of the reflex. Maximum resting anal pressure and maximum squeeze pressure in patients who were not improved by anorectal myectomy were slightly greater than those who had a good result. However, these differences were not statistically significant. No other parameter measured before operation had any prognostic value.

It has been suggested that manometric studies are diagnostic of Hirschsprung's disease and that rectal distension causes contraction rather than relaxation of the internal sphincter[3]. Nevertheless, we found that there were four patients with Hirschsprung's disease in whom the recto-anal inhibitory reflex was preserved and six histologically normal subjects in whom the reflex was absent. Therefore, lack of the recto-anal inhibitory reflex may not be diagnostic of Hirschsprung's disease.

Of the 11 patients who had persistent constipation after anorectal myectomy four had prolonged transit times and eventually underwent total colectomy whilst 7 have been managed conservatively. None of those having a colectomy and ileorectal anastomosis became incontinent despite their previous myectomy. We have not experienced any recurrence of constipation in the patients who achieved a good result during a follow up of between 6 and 28 months, but prolonged follow-up might be needed to ensure that these early results are maintained.

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Paper accepted 18 December 1986

Br. J. Surg. 1987, Vol. 74, May,
377–380

Adenomatous polyposis: an association with carcinoma of the thyroid

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A review of the St Mark's Hospital Polyposis Registry has revealed an association between adenomatous polyposis (familial polyposis coli) and thyroid carcinoma. Even though full clinical information was unavailable on all patients in the registry, it is evident that young women (below 35 years of age) are at particular risk of developing thyroid cancer, mainly of a papillary type, their chances of being affected being approximately 160 times that of normal individuals. All patients with adenomatous polyposis should thus have regular thyroid examination.

Keywords: Adenomatous polyposis, thyroid carcinoma

Adenomatous polyposis (familial polyposis coli) is known to be associated with multiple osteomas, epidermoid cysts and fibromas of cutaneous and subcutaneous origin (Gardner's syndrome) as first described in 1953[1]. This syndrome was later expanded to include desmoid tumours[2], wound fibromatosis, abnormal dentition[3] and odontomas[4]. Extracolonic alimentary tumours associated with adenomatous polyposis are gastric and small bowel adenomas[5,6] and peri-ampullary carcinoma[7]. Many other malignancies have been reported in association with adenomatous polyposis including lesions of the central nervous system[8], transitional-cell carcinoma of the bladder[9], hepatoblastoma[10] and also a characteristic pigmentation of the skin[11]. It is unclear if some or all of these are coincidental occurrences or genetically determined tumours. Carcinoma of the thyroid gland has been reported sporadically in patients with adenomatous polyposis and one such patient under our care prompted a review of the St Mark's Hospital Polyposis Registry to determine the incidence of thyroid carcinoma and whether an assocation exists between these two conditions.

Patients and methods

The St Mark's Hospital Polyposis Registry was commenced in 1925 and now contains records of 998 patients who are considered to have adenomatous polyposis. The criteria for inclusion are:

(1) A family history of adenomatous polyposis.
(2) A colon with or without evidence of malignancy which usually contains at least, but usually more than, 100 polyps shown to be adenomatous on histological examination.

The Registry is divided into two groups, each containing patients from the UK and elsewhere.

Group I

This group comprises 316 patients, 186 men and 130 women, 248 of whom have undergone major surgery at St Mark's Hospital and are regularly reviewed at that hospital. The remaining 68 patients have been seen at St Mark's on at least one occasion and, while their clinical histories are not as well documented as those of the 248 having undergone surgery at the hospital, they are in general better documented than Group II patients.

Group II

This group comprises 682 patients, 356 men and 326 women, who are known to St Mark's but whose management is undertaken elsewhere and for whom therefore only incomplete clinical information is available.

A search of all patients' records was made to assess the incidence of thyroid carcinoma and, when possible, histology was reviewed.

Case reports

Group I

Case 1. A Greek women aged 21 years with a family history of adenomatosis polyposis underwent proctocolectomy and ileostomy following discovery of multiple adenomas and a carcinoma of the rectum on her first sigmoidoscopy. Histology showed diffuse adenomatous polyposis and a well differentiated Dukes' C_1 adenocarcinoma of the rectum. One year after colectomy a small swelling on the right side of the neck became more prominent and a total thyroidectomy was performed for a multicentric papillary carcinoma, the largest nodule measuring 2 cm in diameter. No nodes were detected. The patient died three years after colectomy with proven lung metastases from the rectal tumour.

Case 2. An English girl aged 15 years was first seen at St Mark's for routine sigmoidoscopy as her mother had adenomatous polyposis. After several negative examinations, a small adenoma was found and at the age of 19 years, a colectomy and ileorectal anastomosis was performed, the pathology showing more than 800 small adenomas with no evidence of malignancy. Seven years later, following discovery of two nodules in the thyroid, the patient underwent partial throidectomy with removal of a mixed follicular papillary carcinoma (3 cm diameter) and a second papillary carcinoma (0·4 cm diameter). The patient is well at 7 years.

Case 3. An Indian women aged 31 years, first noticed a small nodule in the right lobe of her thyroid, a radio-iodine scan indicating a cold nodule. A few months later after episodes of diarrhoea and fresh blood per rectum, a sigmoidoscopy revealed polyps which histologically were adenomas. A barium enema indicated multiple colonic filling defects and an annular lesion in the proximal transverse colon. Colectomy and ileorectal anastomosis was performed, the histology showing a Dukes' B well differentiated carcinoma of the transverse colon with a second superficial Dukes' A lesion in the sigmoid. The remainder of the colon showed multiple adenomas. At the age of 34 years, the patient underwent right partial thyroidectomy for enlargement of her thyroid nodule; histology showed a well differentiated encapsulated papillary carcinoma 3 cm in diameter. This patient is well 13 years later.

Case 4. A 23-year-old English woman noticed a lump in her neck and underwent total thyroidectomy for a multicentric papillary adenocarcinoma. Adenomatous polyposis was subsequently diagnosed at 27 years of age and a colectomy with ileorectal anastomosis was performed the same year. This patient is well 19 years later.

Group II

Case 5. A white South African woman aged 20 years, presented with large sebaceous cysts on her scalp and a multinodular goitre. Barium enema was normal but sigmoidoscopy showed multiple small polyps. At that time, thyroidectomy was performed for carcinoma of the thyroid (precise histology not known) but surgery for the polyposis was deferred. The patient's mother had undergone laparotomy aged 40 years for carcinomatosis peritonei and hepatic metastases of unknown primary site.

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Table 1 *Number and sex distribution of thyroid carcinoma in patients with adenomatous polyposis*

	Group I Seen at St Mark's			Group II Known to St Mark's			Groups I and II Combined results		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
Number of patients	186	130	316	356	326	682	542	456	998
Number with thyroid cancer	0	4 (3·1%)	4 (1·3%)	0	3 (0·9%)	3 (0·4%)	0	7 (1·5%)	7 (0·7%)

Case 6. An English girl, aged 16 years underwent thyroidectomy for carcinoma of unknown type followed by radiotherapy. At 28 years of age, adenomatous polyposis was diagnosed and anterior resection performed, revealing two carcinomas of the sigmoid colon with polyposis.

Case 7. An English girl underwent colectomy and ileorectal anastomosis at 17 years of age; an exostosis of the frontal sinus and an epidermoid vulval cyst were noted. At the age of 34 years, a left hemithyroidectomy was performed for a thyroid swelling. Histological classification was difficult but it was concluded that this was a low grade carcinoma with local invasion which had been totally removed. The patient is alive and well 11 years later.

Results (*Table 1*)

Groups I

Of the 316 patients in Group I, 4 of the 130 women (3·1 per cent) have developed proven thyroid carcinoma; no thyroid tumours were evident in the men. All 4 women were under 35 years of age at thyroidectomy and all had a papillary pattern of thyroid carcinoma.

Group II

In Group II, 3 of the 326 women (0·9 per cent) were found to have had thyroid carcinoma but again no men were affected. Histology is unavailable in two cases and the third is a malignant lesion of indeterminate type.

Groups I and II combined

Combining the results from both groups gives a 1·5 per cent incidence of thyroid carcinoma in women (7 out of 465 patients).

Discussion

There are geographical and sex differences in the incidence of carcinoma of the thyroid. The annual rates of newly diagnosed cases of thyroid carcinoma in England and Wales are 0·9/100 000 men and 2·4/100 000 women[12] whilst comparable USA figures are 2·1/100 000 for men and 5·2/100 000 for women[13]. In Japan, the combined estimate is 1·4/100 000[14]. Studies from the Mayo Clinic in 1969[15] suggested an increase in the incidence of thyroid carcinoma over two decades in the USA, from 2·5 to 3·6/100 000 population. This was generally attributed to the occurrence of radiation induced cancers, a concept supported by Danish figures over the same period[16].

The World Health Organization classification of thyroid tumours[17] demands distinction between 'occult' papillary carcinoma (clinically non-apparent and only discovered histologically) and 'minimal' thyroid carcinoma (less than 1 cm in diameter, clinically apparent and possibly detectable by specific thyroid imaging). Occult papillary carcinoma may metastasize to local nodes but distant metastases rarely occur[18]. There are differences between both the clinical and the autopsy prevalence of thyroid tumours and between various autopsy series, ranging from 17·9 per cent in a Japanese population previously exposed to nuclear radiation[19] to 2·8 per cent in a USA series[20]. These variations are explained by either different environmental factors in the population under study or differing histological techniques, in particular the depth of histological sectioning.

All patients in our study had clinically apparent tumours (more than 1 cm diameter) and none of the thyroid tumours reported were occult or minimal. We have no autopsy evidence on patients with adenomatous polyposis which would indicate the frequency of these smaller lesions.

Thyroid histology has been reviewed in the 4 patients in Group I, all of whom show papillary adenocarcinoma and were all in women below 35 years of age. Papillary thyroid carcinoma has a peak incidence in the third and fourth decade and a female:male rate of 3:1. Papillary lesions account for approximately 60 per cent of all thyroid neoplasms[21,22] and approximately 80 per cent of thyroid neoplasms in the group below 40 years of age[23]. Less than half of all papillary lesions present below the age of 40 years[24].

The St Mark's Hospital Registry is a cumulative index over 60 years and the mean period for which each patient has been documented is approximately 20 years. The annual incidence of all malignant neoplasms of the thyroid in women of all ages in England and Wales is 2·4/100 000 population[12]. The expected cumulative incidence of thyroid carcinoma for women in the general population over a 20 year period will thus be (20 × 2·4) 48/100 000 assuming a constant annual rate of new tumour development. The cumulative incidence of thyroid carcinoma amongst St Mark's female patients is (4/130) 3077/100 000 in Group I and (3/326) 920/100 000 in Group II giving a combined incidence of 1535/100 000 over 20 years. All our patients and those reported by others were aged between 15 and 34 at the time of diagnosis of their thyroid carcinoma (*Table 2*). There are 83 women aged 15–34 years in our Group I patients. The cumulative incidence of thyroid carcinoma in this group when compared with the same age group in the general population over this 20-year period is thus (4/83) 4819/100 000 *versus* 30/100 000 (1·5/100 000 new cases per annum in the general population)[12]. From these calculations in the general population a young female patient with adenomatosis polyposis can be seen to have a 160 times greater than expected chance of developing a thyroid carcinoma before the age of 35. There are several possible sources of error in arriving at this conclusion. The average age of the St Mark's Hospital thyroid patients is less than that of the general population which may be a real finding or an artefactual consequence of the decreased life expectancy of polyposis patients. Furthermore, not all the St Mark's patients have so far been followed beyond 34 years of age. The actual incidence of thyroid carcinoma in the general population is changing and probably increasing[15,16] and we have taken retrospectively over the last 20 years the highest estimate based on UK figures (48/100 000) which may be an inflated estimate. The increased surveillance of polyposis patients might lead to an increased detection rate of thyroid carcinoma but from intuitive numerical reasoning, given the low prevalence of thyroid carcinoma, it is surprising that there should be any cases detected in the polyposis patients. Given the large difference in rates between the two populations and the fact that several of these factors would tend towards an underestimate of the true difference, there seems little doubt that adenomatous polyposis patients are more likely to develop thyroid carcinoma than the population in general with younger women being at particular risk. In reaching this conclusion the results from Group II patients have been ignored as the lower incidence in this group compared with Group I is most likely to be due to our inadequate clinical data on this more

Table 2 *Summary of all known patients with thyroid carcinoma and adenomatous polyposis*

Study (Reference)	Sex	Age at		Extracolonic manifestations
		Thyroid surgery	Diagnosis of polyposis	
Crail (25)	M	24	24	Died at 24 years. Medulloblastoma
Camiel (27)	F	19	28	Gardner's syndrome
	F	20	29	Gardner's syndrome
Smith (28)	M	29	39	
Smith (29)	F	19	26	
Alm (30)	F	Unknown		
	F	Unknown		
Keshgegian (31)	F	21	14	Odontoma, supernumary tooth, epidermoid cysts, adenomyoma of stomach
Hamilton (32)	F	18	17	
Lee (33)	F	23	32	
Delamarre (34)	F	27	33	
	F	26	21	
Thompson (35)	F	24	22	Benign gastric polyps
Present study	F	22	21	
	F	26	19	
	F	34	31	
	F	23	27	
	F*	20	20	Sebaceous cysts
	F	16	28	
	F	34	17	Exostosis of frontal sinus, epidermoid vulval cyst

* This patient previously reported by Raynham and Louw[26]

geographically diffuse group of patients. However, if the same calculations are applied to Group II the actual incidence of thyroid carcinoma is 68 times that expected and if Group I and II patients are combined the incidence is 101 times that expected.

The association between adenomatous polyposis and thyroid cancer is supported by several isolated case reports[25–35] (*Table 2*). One of those reported from South Africa is included in our Group II patients[26]. The only other series of adenomatous polyposis patients reported is from Sweden[30] in which two thyroid tumours were found in 169 women and no thyroid tumours in 171 men. No thyroid cancers were found in the men in our study and this, taken with all the previous reports in adenomatous patients showing an overall ratio of 2 men to 11 women, may reflect the sex ratio of the disease in the general population but the numbers are too small to draw firm conclusions.

The thyroid tumours have occurred in the younger age group with all patients having had thyroidectomy before the age of 35 years. There is no clear pattern of timing of presentation of the thyroid tumour in relation to the diagnosis of adenomatous polyposis, some occurring simultaneously. Whilst thyroid histology has not always been available there is a clear preponderance of papillary lesions.

The implications of an association between adenomatous polyposis and thyroid carcinoma are evident. Patients with adenomatous polyposis need regular review, not only to monitor progression of the polyposis, many of them having had preservation of the rectum after colectomy but also to assess them for associated neoplasms. This should now include careful palpation of the thyroid gland and cervical lymph nodes especially in the young female group with early resort to imaging, fine needle aspiration and, if necessary, biopsy where clinical doubt exists over the presence or nature of thyroid swellings.

Acknowledgements

We are grateful to Dr S. Wilson, Professor I. Doniach and Dr M. El Mahallawy for reviewing the histology and pathological advice. We are indebted to Dr J. Wadsworth for statistical assistance and Miss M. Petrie for typing the manuscript.

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Paper accepted 20 December 1986

Br. J. Surg. 1987, Vol. 74, May, 381–383

Mucosal proctectomy and colo-anal anastomosis for distal ulcerative proctocolitis

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Four patients with long-standing symptomatic ulcerative colitis confined to the left colon and rectum were treated by resection, mucosal proctectomy and colo-anal sleeve anastomosis. There was no operative mortality or anastomotic leakage. Follow-up has ranged from 12 to 66 months (mean 52 months). Loose bowel motions with urgency and frequency of defaecation were troublesome postoperative symptoms. Recurrence of the colitis in the neorectum with extension into the proximal colon occurred in all patients within 3 to 11 months (mean 6 months) of operation. This necessitated total proctocolectomy with ileostomy in three patients (mean 18 months postoperatively). In the fourth patient the recurrence is medically controlled without a stoma more than 5 years after operation. This operation is unsuitable for the treatment of segmental ulcerative proctocolitis.

Keywords: Ulcerative proctocolitis, colo-anal anastomosis, ileostomy, anorectal function

The conventional surgical treatment of diffuse idiopathic ulcerative colitis is by proctocolectomy with either ileostomy or, in carefully selected patients, ileo-anal anastomosis with a pelvic reservoir[1]. In approximately 30 per cent of patients with ulcerative colitis the disease remains confined to the rectum and sigmoid colon[2–4]. The treatment of segmental colitis by excision of only the affected part of the large bowel remains controversial. Clark and Ward[5] reported the results of excision of the rectum and distal sigmoid colon with the establishment of a permanent colostomy in four patients. Although all four patients eventually developed proximal extension of the colitis, only one of them required colectomy and ileostomy after 5 years. A report of four similar patients from St. Mark's Hospital made a case for limited excision[6]. In Stahlgren and Ferguson's[2] series of 18 patients treated in this way, 7 required total colectomy and ileostomy by 5 years. The same authors reported good results with primary resecton and anastomosis in the treatment of right-sided colitis. Furthermore, there are conflicting reports of the outcome of treating distal segmental ulcerative proctocolitis by excision of the affected bowel and restoration of intestinal continuity by caeco-anal anastomosis[7,8]. We report the late clinical results in four such patients treated by Parks' colo-anal sleeve anastomosis[9].

Patients and methods

Details of the four patients treated between 1979 and 1985 are shown in *Table 1*. The mean age was 42 years and the mean duration of symptoms was 10 years. The symptoms included bloody diarrhoea, frequency and urgency of defaecation and occasional incontinence. All four patients had undergone prolonged and intensive medical therapy but these incapacitating symptoms were uncontrolled by conservative measures. The diagnosis was established by clinical, histological and radiological features. All patients had undergone repeated colonoscopic assessment of the large bowel with multiple biopsies. These had shown a distal ulcerative proctocolitis clearly demarcated on histological criteria from heathly proximal colon. The proximal extent of disease is shown in *Table 1*.

Only in one patient (patient 3) was there any evidence of proximal progression of the disease over the years from initial diagnosis to operation. In this patient the colitis had extended from the sigmoid colon to the descending colon. These patients were under surveillance by the inflammatory bowel disease medical review clinic of the Gastrointestinal Unit and were referred as possibly suitable for sphincter preservation by segmental colorectal excision. They were thought particularly suitable for a colo-anal anastomosis because of the limited extent of their left-sided colitis and because this had remained anatomically static for several years (*Table 1*). In addition three of the patients were relatively young and reluctant to accept a permanent stoma. Details of the technique are described elsewhere[9–11].

The proximal site of section was determined by the pre-operatively determined extent of the colitis. 'Protecting' loop transverse colostomies[12] were fashioned in the right upper quadrant in two patients and loop ileostomies in the other two. Stomas were closed when the anastomosis was clinically healed, and any stenosis had been dilated. The mean time to closure of the stoma was 15 weeks. Follow-up has ranged from 12 to 66 months (mean 52 months). Three patients have been followed-up for more than 5 years. At each clinic visit continence and bowel function were assessed objectively and the distal bowel examined by sigmoidoscopy.

Results

There was no operative mortality. The early complications (one fissure-in-ano, one thrombosed haemorrhoid, one stomal haemorrhage, one subacute obstruction) were managed successfully by conservative measures. Frequency of defaecation in the early period after closure of the protecting stoma was a common feature. The late complications are of more interest. There was one anastomotic stricture which required repeated dilatation (patient 2). Symptomatic recurrence of the colitis occurred in all four patients (mean time 6 months after operation). Diarrhoea with frequency, urgency and occasional incontinence were the predominant symptoms.

In three patients this relapse did not respond to medical management and required total proctocolectomy with ileostomy. This was performed 24, 12 and 18 months after the colo-anal operation. The histopathology of the excised colon showed involvement of the entire colon in all three patients. The fourth patient has similar symptoms but is reasonably controlled by medical measures more than 5 years after operation. She is continent of solid stool but has occasional incontinence with loose bowel motions and wears an incontinence pad. The precise proximal extent of the colitis in this patient is not known.

There was no apparent relationship between the time to recurrence of the colitis and the pre-operative extent, severity or progression of the disease in this small group.

At the initial operation the macroscopic extent of disease in the resected specimen related accurately to the pre-operative assessment by colonoscopy and biopsies. A clear line of demarcation was easily seen between healthy and affected colon in the excised specimen (*Figure 1*).

Table 1 *Clinical details of four patients with limited distal ulcerative colitis*

Patient no.	Age	Sex	Proximal pre-operative extent of colitis	Duration of symptoms (years)	Symptoms/ complications	Protecting stoma and time to closure (weeks)	Time to extension of colitis postoperatively (months)	Time to proctocolectomy and ileostomy postoperatively (months)
1.	28	F	Sigmoid colon	9	Diarrhoea, haemorrhage, stricture (13 cm)	Loop transverse colostomy (15)	11	24
2.	39	F	Descending colon	18	Diarrhoea, haemorrhage, polyp	Loop ileostomy (20)	5	12
3.	59	F	Descending colon	10	Diarrhoea, haemorrhage, abdominal pain	Loop ileostomy (11)	3	—
4.	40	M	Rectum	3	Diarrhoea, haemorrhage, abdominal pain	Loop transverse colostomy (15)	6	18

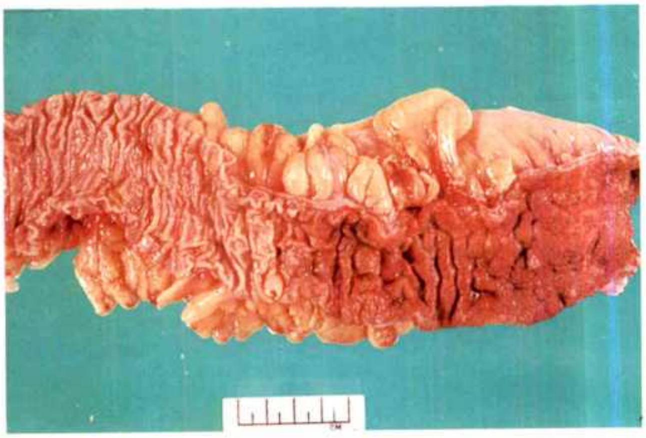

Figure 1 *Resected colon showing the clear demarcation between the inflamed and healthy mucosa*

Discussion

The rectum is the commonest site of involvement in ulcerative colitis and the only site in approximately 20 per cent of cases[1]. So-called 'idiopathic proctitis' differs from ulcerative colitis only in the extent of bowel involvement and appears to carry a better prognosis[2-4]. Lennard-Jones *et al.*[3] followed up 100 patients with 'idiopathic proctitis' of whom only four later came to operation. Proctocolectomy is the accepted treatment for uncontrolled colitis affecting the colon diffusely or segmentally.

Clark and Ward[5], however, concluded that where incapacitating symptoms result primarily from rectal involvement, treatment by excision of the rectum is worthy of consideration. They treated four such patients by rectosigmoid excision and colostomy. All these patients developed symptomatic proximal extension of the colitis but only one needed to have a total colectomy with ileostomy at 5 years. Their maximum follow-up was 6 years.

A similar series from St. Mark's Hospital[6] reported two recurrences out of four but they were able to be controlled medically. Stahlgren and Ferguson[2] treated 18 patients with rectosigmoid excision and terminal colostomy. Seven patients required completion of the colectomy with ileostomy by 5 years and a total of 10 patients by 10 years. They, nevertheless, argued that this approach was justified on the assumption that colestomy, even if only for a few years, is preferable to ileostomy. Other workers, however, have recommended ileostomy as a far easier stoma to manage when rectal excision is required[5,13], and there is some evidence for this preference[14]. The results of restorative caeco-anal pullthrough operations are somewhat conflicting. Johnston *et al.*[7] reported four out of five early failures although Roediger *et al.*[8] appear to suggest promising long-term results.

We have treated four patients by excision of the left colon and colo-anal sleeve anastomosis, thus precluding the need for a permanent stoma. This technique, first described by Parks[9,10], has been used for a variety of rectal conditions including large rectal haemangiomas, extensive villous adenomas of the rectum, rectovaginal fistulae, low rectal carcinomas and severe radiation injury to the rectum[9,11,15]. However, its validity in the treatment of segmental proctocolitis does not appear to have been recorded. The patients chosen for this study represented a very select group with segmental left-sided colitis and were unwilling to accept a stoma. Therefore, it was felt to be justifiable to perform a less extensive procedure than an ileo-anal pouch operation. Acceptable results have been previously reported with limited excision for right-sided colitis[2,16-18].

Furthermore, our long-term results for radiation proctocolitis treated by this procedure appeared encouraging[11]. Several factors may be implicated in the aetiology of the poor functional results. The early postoperative symptoms probably represent reduced rectal capacity and might be expected to improve[19]. Transposition of the transverse colon to the pelvis can itself result in a permanent hypermotile state in 10–15 per cent of patients[20]. However, extension of the colitis was largely responsible for the disappointing results, further aggravating symptoms by its effects on colorectal motility[21,22] and stool consistency. Some internal anal sphincter dysfunction may also be present due to stretching of this muscle for the peranal anastomosis[23,24].

It must be noted, however, that one patient manages well without a stoma more than 5 years after operation. This is in keeping with the observations of other studies of limited excision[2,3,6,11,12,16-18] where some patients achieved months or years of symptomatic remission. Unfortunately, it is not possible to select these patients pre-operatively as the reasons for recurrence remain unknown. Late results of the treatment of severe distal radiation proctocolitis by this operation are considerably better compared with the ulcerative colitis group[11]. This is simply due to the different aetiological background in these inflammatory bowel diseases.

Despite the small number of patients reported, this long-term study suggests that colo-anal sleeve anastomosis does not have a place in the surgical treatment of segmental proctocolitis. Alternatives such as proctocolectomy with ileostomy or, preferably, ileo-anal anastomosis with a pelvic ileal reservoir[25,26] are recommended.

Acknowledgements

J.S.V. was supported by a Wellcome Trust Research Grant No. 12196 14 L and the British Digestive Foundation (Scottish Appeal).

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Paper accepted 30 November 1986

Br. J. Surg. 1987, Vol. 74, May,
384–386

Postanal repair and intersphincteric Ivalon sponge rectopexy for the treatment of rectal prolapse

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Twenty-four consecutive patients (mean age: 74 years) with complete rectal prolapse, fifteen of whom were incontinent of solid stool, have been treated by postanal repair and intersphincteric Ivalon sponge rectopexy. There was no operative mortality, or serious morbidity. There was one recurrence of complete prolapse which occurred 14 days after operation. The other 23 patients have been followed for up to 4 years. All patients who were incontinent of solid stool pre-operatively have been rendered continent. This type of operation may be the treatment of choice in the elderly, where an abdominal procedure is considered unwise and in cases of rectal prolapse associated with faecal incontinence.

Keywords: Rectal prolapse, faecal incontinence

Complete rectal prolapse is associated with faecal incontinence and occurs predominantly in the elderly. Many procedures have been designed for the treatment of rectal prolapse and may be divided into abdominal and perineal procedures. It is widely held that an abdominal procedure is the best method to reduce and fix a complete rectal prolapse. The operations in common use are the Ivalon sponge rectopexy (Wells[1]) and the Marlex mesh rectopexy (Keighley[2]). The results of abdominal procedures are good with regard to control of the prolapse but the problem of associated faecal incontinence is far from solved with more than a third of patients remaining incontinent despite a successful rectopexy[2,3–5]. A proportion of these patients may require a secondary continence procedure[2,6]. The concept of a perineal procedure to reduce and fix a complete rectal prolapse is nearly 100 years old and there has been a recent revival of interest in this approach; in particular the perineal rectopexy described by Wyatt[7] and the Delorme procedure[8], whose advocates suggest that it is the preferred procedure in the elderly and frail. The popularity of Thiersch's circumferential wiring and its modifications has waned over the years because of poor results achieved in control of the prolapse and concomitant difficulties with defaecation following the procedure[9]; often the encircling materials fracture, or ulcerate through the skin, requiring repeat procedures to be undertaken[10,11].

All previously described procedures have been designed with the primary aim of treatment of the prolapse and not for their effect on associated faecal incontinence.

We describe a new technique designed with the aim of restoring continence, in addition to the treatment of the prolapse. It combines a postanal repair with an Ivalon sponge rectopexy performed via the intersphincteric plane.

Patients and methods

Patients

Twenty-four patients (twenty-two women) aged 41–93 years (mean: 74 years, median: 76 years) had the operation between June 1982 and May 1986. Fifteen of the patients were incontinent of solid stool. Five had had previous surgery for prolapse, two a Wells Ivalon sponge rectopexy and four the insertion of Thiersch wires. Seventeen of the twenty-four patients (70 per cent) were over 70 years at the time of the operation.

Surgical procedure

Patients were prepared for surgery with castor oil and rectal washouts. Antibacterial chemoprophylaxis with co-trimoxazole 960 mg and metronidazole 500 mg IV was given peroperatively and for 24 h postoperatively. Under general or spinal anaesthesia the patient was placed in the lithotomy position and following standard skin preparation adrenaline 1:300 000 in 0·9 per cent NaCl was infiltrated into the subcutaneous tissue between the coccyx and the anus. A curved postanal incision was made bisecting the line between the anus and coccyx, convex posterior. The anterior flap of skin and subcutaneous tissue was raised to expose the sphincter complex. The intersphincteric plane was then developed using blunt and sharp dissection. Waldyer's fascia was divided above the puborectalis to enter the retrorectal space. This space was developed as high as possible by mobilizing the rectum from the sacral fascia, allowing the sacral curve to be seen. A 10 × 12 cm rectangle of Ivalon sponge was placed on to the sacrum. The rectum was allowed to fall back towards the sacral curve, resting on the bed of Ivalon sponge.

A standard postanal repair[12] was then performed, using braided nylon suture (Nurilon, Ethicon) to form a lattice between one side of the levator ani and the other, starting as high as possible at the ileococcygeus muscles. In separate layers further lattice sutures were inserted to draw together the pubococcygeus, puborectalis and finally the external sphincter muscle posterior to the anal canal. It was important not to put excess tension in these lattice sutures in the upper layers of the levator musculature. The wound was closed with silk sutures after trimming of the redundant skin to gain a perfect closure.

Following surgery the patients were nursed in a lateral position for two days. From the third day two glycerine suppositories were inserted daily to ensure the patient had a comfortable bowel action and to reduce straining at stool.

Follow up was at 1 month, 3 months and 6 monthly thereafter. Assessment of continence was by direct questioning and whether patients required continence pads.

Results

Perioperative

The operation was well tolerated by this elderly group of patients. Three patients had the operation under spinal anaesthetic. In two patients the posterior wall of the rectum was breached during mobilization and the defects were closed by suture. These patients had not had previous surgery for prolapse. The operation time was between 45 min and 1 h. There was minimal intra-operative blood loss and no pulmonary or cardiovascular complications.

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Table 1 *Results of operations for rectal prolapse*

Procedure	Reference	No. of patients	Mortality	Recurrent prolapse	Mucosal prolapse	Incontinent of solid stool (Pre-operative)	Incontinent of solid stool (Postoperative)	Incontinence (postoperative/pre-operative) %
Ivalon sponge rectopexy	Morgan *et al.*[3]	150	4	3	11	83	40	48
	Penfold and Hawley[4]	101	0	3	31	70	23	32·8
	Anderson *et al.*[5]	40	1*	1	6	16	7	43·7
	Anderson *et al.*[14]	42	0†	1		20	5	25
Marlex mesh rectopexy	Keighley *et al.*[2]	100	0	0	4	67	24	35·8
Thiersch wire	Goligher[9]	19	0	10	3	5	4	80
Delorme's operation	Christiansen and Kirkegaard[8]	12		2		2	1	50
Perineal rectopexy	Wyatt[7]	22	0	1	3		1‡	
Postanal repair and intersphincteric Ivalon sponge rectopexy (present series)		24	0	1	4	15	0	0

* Only 37 reviewed; † only 37 reviewed; ‡ incontinence classified as 1 major and 4 minor

Early results

There was one recurrence of complete prolapse at 14 days following surgery. Fourteen days after the recurrence the patient underwent an abdominal rectopexy by the Loygue[13] procedure which was successful. There were eight cases of superficial wound infection. Healing was then by second intention, requiring delay in discharge by 2 or 3 days. The average stay in hospital was 14 days.

Late results

Twenty-four patients have been followed for 2–48 months (mean: 21 months). During this time five have died of unrelated problems, at 2, 11, 30, 36 and 42 months after operation. All returned home, and none had recurrence of the prolapse. In the remaining 19 patients there has been no recurrence of the prolapse, except the patient mentioned previously. Four patients had minor mucosal prolapse treated successfully by band ligation. Two patients had a late infection of the wound requiring the removal of a superficial Nurilon suture. The 15 patients who were incontinent before operation have been rendered continent to solid stool, 13 are continent to liquid stool and 8 to flatus.

Discussion

Abdominal rectopexy is the operation against which other methods for the treatment of rectal prolapse are judged. Complete rectal prolapse occurs predominantly in women with a peak age incidence in the seventh decade[9]. There is evidence that the age of presentation is on the increase: the mean age of our series (74 years) is almost 10 years higher than the mean reported by Naunton-Morgan[3] and agrees with the series reported by Wyatt[7]. Therefore, it is of no surprise to find a revival of interest in the perineal approach with the aim of avoiding a laparotomy in this elderly and frail group, while attempting to offer an equally effective procedure to abdominal rectopexy for control of the prolapse. Associated faecal incontinence varies in recorded series from 11 to 81 per cent[2-4,13]. In these series a third or more of patients remain incontinent despite successful reduction and fixation of the prolapse. The results of the procedure described have, to date, fulfilled the aims (*Table 1*). They compare with those of abdominal rectopexy and compare well with perineal rectopexy, with no mortality and only one recurrence during the present period of follow-up. The effect on associated faecal incontinence is encouraging.

Eight of the twenty-four patients had superficial wound infections, which appeared as redness and oedema of the wound edges, requiring the removal of skin sutures and the application of antiseptic dressings to promote healing. This wound infection rate of 33 per cent is similar to that reported by Lewis[15] in his series of postanal repair in the elderly, wound infection being 36 per cent and wound necrosis 26 per cent. No patient had difficulty in evacuating the rectum in the postoperative period, a problem sometimes encountered after postanal repair. The daily use of glycerine suppositories after the operation ensured a comfortable bowel action and reduced straining at stool.

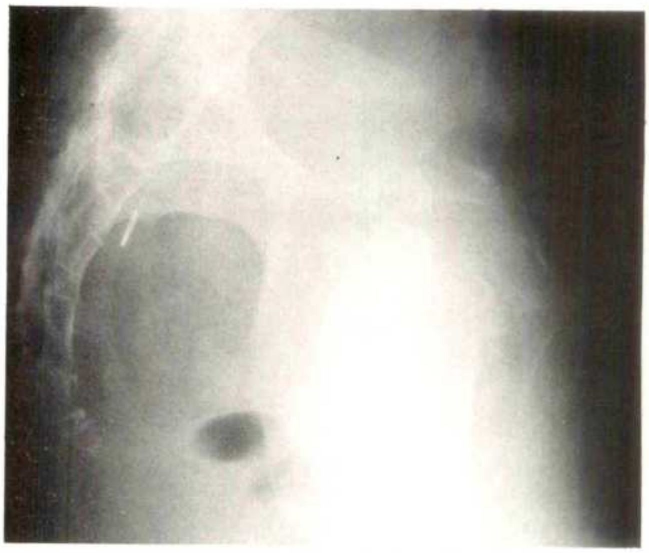

Figure 1 *A lateral X-ray of the pelvis showing a clip marking the apex of the dissection, and the upper limit of the Ivalon sponge insert*

There is still some discussion as to the effect of Ivalon sponge on body tissue and the degree of fibrosis it may cause. Schofield[16] showed Ivalon sponge induced a solid, non-rigid fibrous tissue with incorporation of the sponge into the tissue. Boutsis and Ellis[17] report the formation of a thick fibrotic tissue in their Ivalon-wrap procedure. In another series, in which repeat operations for rectal prolapse have been performed, this fibrosis has been documented[4]. It is on this fibrosis that we rely to anchor the rectum to the sacral curve as the sponge is simply laid into position and not sutured. To determine the extent of mobilization of the rectum we placed marker clips (Ligaclip, Ethicon) at the upper end of the dissection. Later X-rays show this to be at the level of the third sacral body (*Figure 1*).

Parks'[12] original paper on the postanal repair showed poor results when used alone in patients with rectal prolapse and faecal incontinence, where rectal prolapse was the predominant problem. Half of the patients in this sub-group of his series had a recurrence of the prolapse and required a rectopexy. Patients in the seventh and eighth decade were largely excluded from this series because of poor early results in this age group. In a recent series where the postanal repair was used in an unselected and elderly group of 19 patients who had idiopathic faecal incontinence, the results compared well with the original series of Parks supporting the conclusion that advanced age alone is not a contra-indication to postanal repair.[15]

In combining the postanal repair with an intersphincteric Ivalon sponge rectopexy we have demonstrated a safe and effective procedure for the treatment of rectal prolapse which deals effectively with the problem of associated faecal incontinence and obviates the need for a secondary continence procedure. It may be the method of choice for the treatment of the elderly patient with rectal prolapse and incontinence.

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Paper accepted 25 January 1987

Br. J. Surg. 1987, Vol. 74, May,
387–389

Surgery for necrotizing enterocolitis

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Thirty-seven patients who had necrotizing enterocolitis and required emergency surgical intervention are reviewed. The indications for surgery were intestinal perforation (28), intestinal obstruction (7), clinical deterioration (1) and persistent rectal bleeding (1). The initial procedure was percutaneous peritoneal catheter drainage (13), intestinal diversion alone (8), intestinal resection (14), laparotomy and biopsy (1) and laparotomy alone (1). Twelve patients developed late intestinal strictures. The overall mortality rate was 35 per cent.

Keywords: Enterocolitis, neonatal surgery

Advances in the management of the low birth weight infant during the last 20 years have resulted in an increased survival. As a result the number of infants who subsequently develop necrotizing enterocolitis has increased, the disease becoming well recognized[1,2]. In patients who require surgery, survival has improved with survival rates between 40 and 60 per cent[3,4]. We present a 14 year experience of patients with necrotizing enterocolitis in whom continued conservative management was considered inappropriate and who required surgical intervention.

Patients

During the period January 1972 to December 1985, 102 neonates admitted to the Regional Neonatal Surgical Unit in the Royal Hospital for Sick Children, Glasgow were diagnosed as having necrotizing enterocolitis (*Figure 1*). This does not reflect the incidence of this disease in the west of Scotland as many neonates have been diagnosed and treated conservatively in neonatal nurseries and intensive care units by the paediatricians or in consultation with paediatric surgeons. Only patients thought likely to benefit from the specialized services of the neonatal surgical unit were transferred. Of the 102 neonates, 37 (36 per cent) required surgical intervention and only these patients will be considered further in this report.

There were 20 boys (54 per cent) and 17 girls (46 per cent). Nineteen neonates were delivered at <36 weeks gestation and sixteen neonates had birth weights of <2 kg. The age of the patients on admission are shown in *Figure 2*. The following potential stress factors predisposing to the development of enterocolitis were identified: lower uterine segment Caesarean section (15), forceps delivery (4), breech (2), endotracheal intubation (9), respiratory distress syndrome (11), umbilical catheterization (10), exchange blood transfusion (5) and congenital heart disease (7). There was no detectable pattern in the organisms isolated from the numerous bacteriological studies. All 37 patients were commenced on antibiotic therapy. The most common combination was penicillin, gentamycin and metronidazole. Eighteen patients (49 per cent) had a course of intravenous nutrition.

Surgical treatment

The reasons for initial surgical intervention as an emergency were: intestinal perforation (28), obstruction (7), clinical deterioration (1) and persistent rectal bleeding (1). The initial procedures on the 37 patients were percutaneous drainage (13), intestinal diversion alone (8), intestinal resection (14), laparotomy and biopsy (1) and laparotomy alone (1).

The 13 infants who had percutaneous drainage were very premature, low birth weight infants and were too sick to withstand formal laparotomy at that time. All had perforation of bowel and the peritoneal cavity was drained by inserting a percutaneous catheter in the lower quadrant under local anaesthesia.

Eight patients had intestinal diversion alone; for perforation in two and extensive disease in six. Ileostomy was carried out in five and colostomy in three.

A total of 14 patients had intestinal resection of whom 10 had resection and proximal diversion by colostomy (6), ileostomy (3) and jejunostomy (1). The other four patients had resection and primary anastomosis. One patient with persistent rectal bleeding had laparotomy and biopsy which confirmed the diagnosis. Another patient had involvement from the duodenum to the rectum. At laparotomy the extent of the disease precluded any treatment and the abdomen was closed. The site of perforation in the patients who underwent laparotomy was in ileum(7), caecum (3), ascending colon (3), transverse colon (5), sigmoid colon (3). Four patients had two perforations and one had multiple perforations.

Results

Of the 13 patients who had percutaneous peritoneal catheter drainage 6 did not require further surgery and the bowel recovered. Subsequently one of these patients died suddenly and gut was seen to be intact at autopsy. Seven patients required further surgery: two died after the second operation to resect

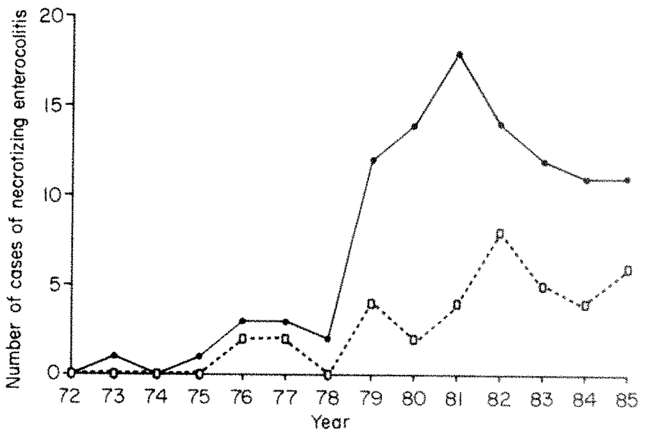

Figure 1 *The total number of patients presenting with necrotizing enterocolitis per year (——), and the number treated surgically (- - -)*

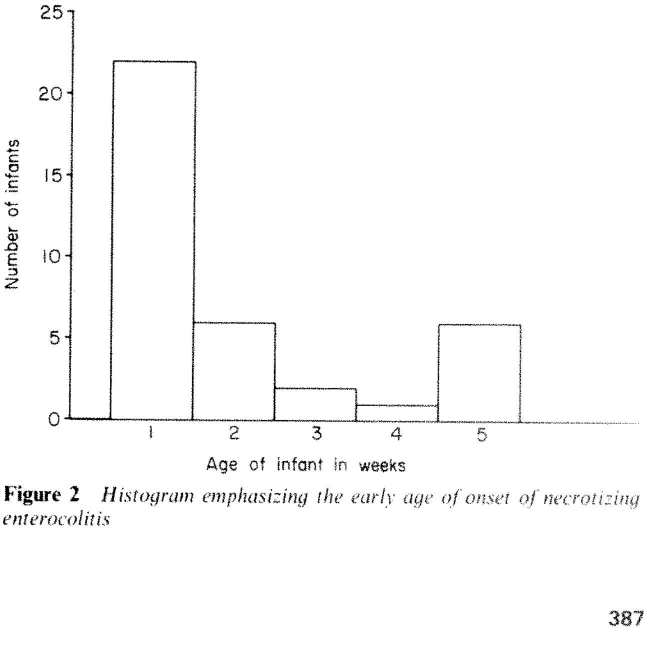

Figure 2 *Histogram emphasizing the early age of onset of necrotizing enterocolitis*

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diseased bowel, while the other five survived operations of resection, diversion and closure of enterostomy. The overall mortality rate for these 13 patients treated initially by percutaneous drainage was 23 per cent.

Six of the eight patients (75 per cent) who had intestinal diversion alone as the initial procedure died. The two survivors (one with perforation and one with extensive necrotizing enterocolitis had resection with anastomosis carried out at their second operations.

The four patients who had intestinal resection and primary anastomosis at their initial emergency operation survived. Two of the ten patients who had intestinal resection and diversion died after the initial surgery. The remaining eight had their enterostomies closed; one of these patients subsequently died. The overall mortality rate for those who had resection was 21 per cent. The patient with persistent rectal bleeding who had laparotomy and biopsy survived while the patient with massive disease who had laparotomy alone died.

Thirteen of the thirty-seven patients died giving an overall mortality rate of 35 per cent. Of the 13 deaths, 3 occurred more than 30 days after surgery but are included in the mortality statistics. The contributing factors to causing death were disseminated intravascular coagulation (5), major congenital heart abnormalities (3), intracranial haemorrhage (2), massive intrapulmonary haemorrhage (1), acute renal failure (1) and respiratory failure due to cor pulmonale (1).

Twelve patients (32 per cent) developed intestinal strictures. The interval between the acute onset and the diagnosis of stricture ranged from 26 to 365 days (meantime 101·5 days). The stricture affected the ascending colon (2), descending colon (3), splenic flexure (3), transverse colon (2) and terminal ileum (2). Only ten patients had late surgery where the strictured segment was excised with primary anastomosis, of whom two died (20 per cent). Of the two patients not submitted to surgery one died from septicaemia and the other patient's symptoms resolved with conservative treatment. Subsequent contrast studies showed complete resolution of the stenotic segment.

Discussion

Necrotizing enterocolitis is a complex disease with many factors contributing to the aetiology. Ischaemic damage to the intestinal mucosa, bacterial colonization and substrate to allow bacterial proliferation are important for the development of the disease. It has also been suggested that defective immunity may have an aetiological role but we have been unable to confirm this[5]. The bacteriology is controversial. In this series as in a previous report[6] we have been unable to identify a specific causative organism. However some workers have implicated a specific bacterium such as *E. coli*[7], *Klebsiella*[8], *Bacteroides*[7,8] and *Clostridia* species[9]. It is generally agreed that the flora in neonates who develop necrotizing enterocolitis is different from that of normal healthy infants and this difference in flora is related to the intensive care environment in which such infants find themselves[10]. Babies with certain risk factors are more likely to develop the disease and often require the specialized facilities of intensive care units. The majority of our patients developed the disease in the first weeks of life. There were six patients older than 4 weeks. All were premature with mean gestational age of 29 weeks.

We have analysed 27 factors in neonates with necrotizing enterocolitis and we were able to identify three factors that appear to be of prognostic statistical significance, namely blood pH, platelet count and the presence of congenital defects[11] while others have tried to identify patients who require early surgical intervention[12]. However, identification of such patients requires early presentation and assesment. Seventeen out of the twenty-eight patients (60·7 per cent) with intestinal perforation in this series had developed the perforation before transfer to the surgical unit. Prediction of outcome can be applied to all necrotizing enterocolitis patients but does not alter management significantly. It is based on objective factors and sequential measurements allow the course of the disease to be followed closely.

Percutaneous drainage of the peritoneal cavity was described previously by Ein *et al.*[13]. Six of our thirteen patients sealed their perforation and required no additional surgical procedures. These results are similar to those of Janik and Ein[14] and show that percutaneous drainage should not be regarded solely as a temporary measure in premature infants. However, seven patients did require further surgery of whom 2 died.

The most common initial emergency operation involved some form of intestinal resection. Four patients had resection with primary anastomosis and all survived. However, like other authors[15,16], we believe that resection with primary anastomosis should be restricted to selected cases and intestinal resection with diversion is regarded as the surgical treatment of choice[15].

Martin and Neblett[17] reported on three patients who survived following intestinal diversion alone for advanced pregangrenous enterocolitis without perforation. Our experience of diversion alone is limited to 8 patients only 2 of whom (25 per cent) survived.

Stricture formation is a well recognized late complication following both medical and surgical management[18-20]. Janik *et al.*[20] estimated that between 6 per cent and 33 per cent of infants with previous enterocolitis develop intestinal strictures. In our series 12 patients (32 per cent) developed intestinal stricture with a mean interval of 101·5 days from the onset of the disease. Ten patients were submitted to surgery of whom 2 died (20 per cent). Other series report mortality rates between 15 per cent and 25 per cent[18-20]. Intestinal stricture like the acute disease still carried an appreciable mortality rate.

From our own results we believe that the acute disease with intestinal perforation should be treated by intestinal resection with proximal diversion or by peritoneal drainage in premature low birth weight infants.

Following the resolution of the acute disease, patients should be followed up for possible stricture formation. Where surgery is required intestinal resection with primary anastomosis is the operation of choice but resection with proximal diversion and subsequent closure of colostomy is an acceptable alternative.

Long term follow-up of surviving patients may reveal serious medical problems, commonly observed in the very low birth weight infants[21].

In this series there was no long term problem with short bowel syndrome. However, two infants developed diarrhoea after excision of a long segment of the colon; both responded to loperamide treatment.

Acknowledgement

We wish to thank the paediatric surgeons at the Royal Hospital for Sick Children for permission to review their cases and Miss Lynn Hilley for typing the manuscript.

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Paper accepted 16 January 1987

Case report

Br. J. Surg. 1987, Vol. 74, May, 389

Carcinoma of the sigmoid colon secondary to a foreign body

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To date no patient has been described with a metal foreign body in association with cancer.

Case report

A 63-year-old man presented with severe diarrhoea. He had been well until 2 months previously. At the time of presentation he was opening his bowels some 20 times a day; he had left iliac fossa pain, some rectal bleeding, and had noticed some weight loss. On examination he looked unwell and was clinically anaemic. He had a tender mass palpable above the left inguinal ligament, but no pelvic masses were palpable on rectal examination. Sigmoidoscopy revealed a tumour at 22 cm, and plain X-ray of the abdomen revealed a large intra-abdominal metal bolt (*Figure 1*). After blood transfusion and bowel preparation the patient underwent laparotomy.

At operation the patient was found to have a 6 inch metal bolt lying inside the sigmoid colon and impacted in the rectovesical pouch at its proximal end. At the distal end of the bolt was a carcinoma invading the anterior abdominal wall. There were also secondary deposits of carcinoma in the liver confirmed by Tru-cut biopsy. The carcinoma was mobilized from the anterior abdominal wall, and the foreign body delivered from the mobilized loop of sigmoid colon through a small incision. The adhesions to the pelvis were divided, and the mobilized loop of bowel resected with end to end anastomosis. Postoperatively the patient made an uneventful recovery. To direct questioning on the ward he admitted that he had passed the bolt per anum some 16 years previously, and had been unable to recover it.

Histology of the specimen revealed an adenocarcinoma which had invaded into the serosal fat and metastasized to the liver although no lymph nodes were involved. The patient died about 6 months later.

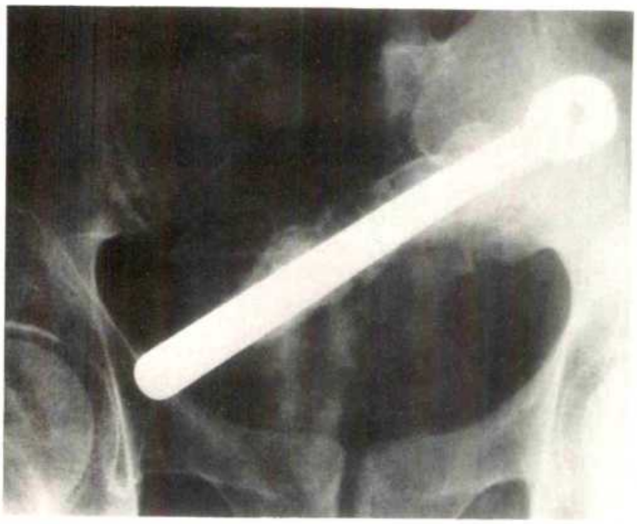

Figure 1 *Plain abdominal X-ray showing the metal bolt lying inside the sigmoid colon*

Discussion

We could not find a previous report of a carcinoma of the colon arising in association with a metallic foreign body although a case has been described of a colon carcinoma arising in association with a bony foreign body[1]. Although it is impossible to prove that the metal bolt induced the carcinoma it seems most probable that it did so since the carcinoma arose exactly over the head of the bolt. Furthermore there are other epithelial surfaces where chronic inflammation can cause cancer, and animal experiments in which a foreign body has been shown to induce carcinoma[2,3].

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Paper accepted 1 October 1986

0007–1323/87/050389–01$3.00

Br. J. Surg. 1987, Vol. 74, May,
390–391

Sliding flap advancement for the treatment of high level fistulae

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The technique of sliding flap advancement for the treatment of high anal fistulae is described. The technique is not suitable for cases with an acute abscess and is reserved for patients with a well-established chronic fistula track. Thirty patients with anal fistulae were treated by sliding flap advancement from 1980 to 1984. Twenty-nine patients had satisfactory results. With a follow-up ranging from 18 months to 4 years no recurrence of fistulae or abscess were observed. The advantages of the advancement flap technique over the staging division technique with application of a seton and over the rerouting technique are discussed.

Keywords: Anal fistula, anus, rectal mucosal advancement

The most universally accepted method for curing all types of anal fistulae is the 'lay-open technique'. The majority of anal fistulae are low lying with the internal opening below the pectinate line and they are easy to treat by a simple fistulotomy. With high fistulae, that is a suprasphincteric, trans-sphincteric or extrasphincteric fistula with a secondary track with its highest level just below the puborectalis muscle and a high anterior fistula in women, the dilemma is how to obtain adequate results without producing any degree of incontinence. To preserve the sphincteric mechanism, high anal fistulae have been treated by a two-stage procedure combined with use of a seton. In most of these cases some loss of muscle function is inevitable.

Parks[1] has devised ways of minimizing this loss of muscle function, but these operations, as Mann and Clifton[2] pointed out, 'are not uniformly successful when applied by others'. Mann and Clifton[2] presented a new method for patients with a well-established high anal and anorectal fistula by rerouting the extrasphincteric portion of the track into the intersphincteric plane with negligible loss of sphincter muscle. This paper presents a method of treatment of high level fistulae with sliding flap advancement combined with laying open or fistulectomy, which might be expected to maintain the sphincter mechanism completely.

Patients and methods

Thirty patients with anal fistulae were treated from 1980 to 1984 at the Teaching Hospital Herford. There were 16 women and 14 men, whose ages ranged from 25 to 68 years (average 47 years). Patients with tuberculosis or inflammatory bowel disease were excluded from this series. Of the thirty patients, three had a rectovaginal fistula, four had a suprasphincteric fistula, four patients had a trans-sphincteric fistula with its highest level just through or below the puborectalis, eight patients had the highest level in the upper portion of the external sphincter and eleven patients had a fistula track in the middle part of the external sphincter muscle.

Twenty-two of the patients had undergone previous operations by other surgeons. Two of the four patients with a suprasphincteric fistula and three of the four patients with a trans-sphincteric fistula with its highest level through or below the puborectalis had undergone more than three operations by other surgeons. These five patients complained of occasional discharge of mucus after their operations. One of the four patients with a suprasphincteric fistula had two operations by other surgeons and complained of discharge of mucus and flatus. All the remaining 24 patients were fully continent for both flatus and faeces.

Technique

As with the rerouting technique of Mann and Clifton[2] this technique is not suitable for cases with an acute abscess and should be reserved for patients with a well established track. After assessing the extent of the fistula by palpation and gentle probing, the skin around the external opening is incised and the incision is developed sufficiently to expose the adjacent borders of the sphincter muscles. After identification of the primary internal opening a small transverse elliptical incision is made around it through the full thickness and deepened outward in a cone shape. The main fistulous track is then cored out up to and through the puborectalis muscle or the external sphincter muscle. The crypt-bearing tissue around the internal opening of the fistula is excised in this way (*Figures 1* and *2*). If there is difficulty in excising the main track, the granulation tissue of the remaining track is scraped with a curette.

Following complete extirpation of the fistula, the internal muscle

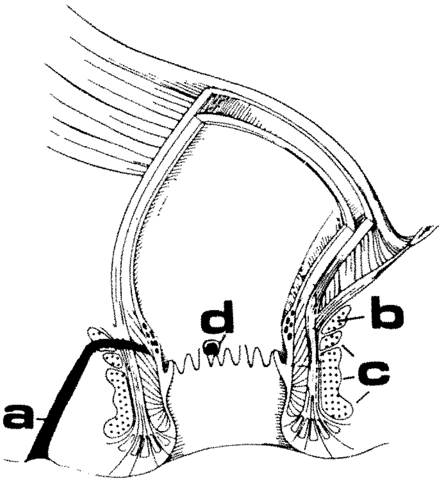

Figure 1 **a** *High trans-sphincteric fistula;* **b** *puborectalis muscle;* **c** *external sphincter;* **d** *internal opening of the fistula*

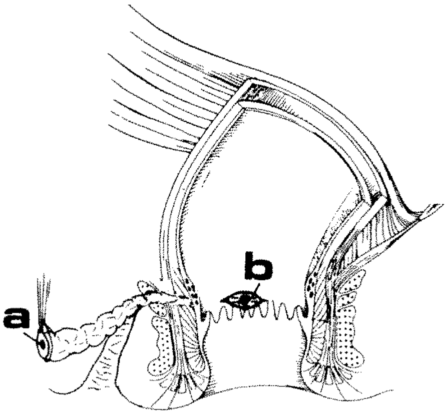

Figure 2 **a** *Excision of the fistulous tract;* **b** *excision of the crypt-bearing tissue around the internal opening of the fistula*

Paper read at the meeting of the German Society of Surgery, Munich 10–13 April 1985

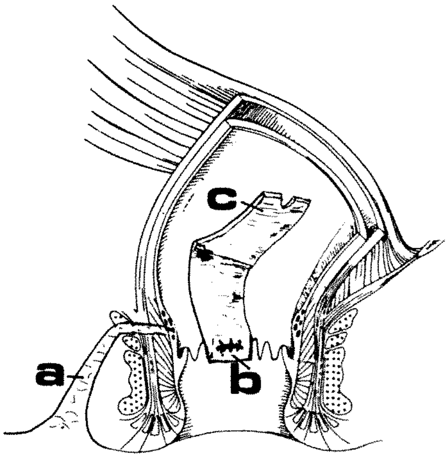

Figure 3 a *The external and trans-sphincteric wound canal;* **b** *muscle closure;* **c** *the flap of mucosa, submucosa and circular muscle undermined proximally*

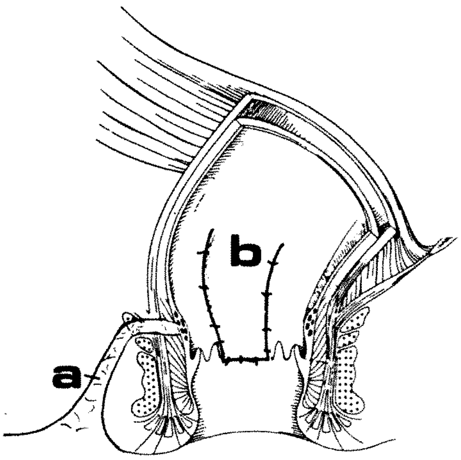

Figure 4 a *The external wound left open for drainage;* **b** *the advanced mucosal flap sutured to the level of the dentata line, distal to the closed internal opening*

layer is closed loosely with 4-0 interrupted polyglycolic acid (Vicryl, Ethicon, 2000 Hamburg, FRG) sutures. Then two oblique upward incisions are made from each corner of the internal wound. A rectal flap consisting of mucosa, submucosa, and circular muscle fibres is outlined around the internal opening extending some 7 cm into the rectum and at least 5 cm cephalad to the fistula opening. The base of the flap should be twice the width of its apex. The flap is undermined (*Figure 3*), mobilized and drawn downwards, and approximated to the lower edge of the mucosa with 4-0 interrupted polyglycolic acid sutures. The mucosal suture line must lie distal to the previous muscle closure. Each side of the mucosal defect is closed with interrupted 4-0 sutures (*Figure 4*).

The external wound has to provide sufficient drainage and is packed loosely. The anal canal is packed for 24 h with foam rubber soaked with Betaisodona (Mundipharma, 1250 Limburg, FRG) (polyvinylpyrrolidone-iod-complex).

In cases with an acute abscess we prefer a staged procedure and pass a seton of braided nylon through the main track instead of coring it out. It has been found in our experience that it is enough to leave the seton for 3 weeks to obtain satisfactory healing and good conditions for closing the internal opening by sliding flap advancement.

Results

One of our three patients with a rectovaginal fistula who underwent treatment by sliding flap advancement developed necrosis of the mucosal flap. This was a technical mistake because care was not taken to create a sufficiently thick flap including parts of the circular muscle. Fortunately this patient came to operation with a covering colostomy and the rectovaginal fistula healed spontaneously.

In the remaining 29 cases the postoperative course was without complications and the wounds healed in 6–10 weeks (average 7·5 weeks). To date, all eight patients with disturbances of continence have reported that the discharge of mucus or of flatus and mucus that existed before the sliding flap advancement operation has not been changed for the worse. The other 21 patients have remained fully continent for both flatus, mucus and faeces since the operation. Except for the patient with the rectovaginal fistula, all the 29 patients were satisfied with the results of the procedure.

With follow-up now ranging from 18 months to 4 years no late complications or recurrence of fistulae or abscess have been observed.

Discussion

The technique of sliding flap advancement for the treatment of high level fistulae has been developed along the lines of the approach described by Elting[3] in 1912 and Laird[4] in 1948 and offers a number of significant advantages. In the staged procedure the setons are left in place for 6–8 weeks and sometimes for several months. This time is necessary for the stimulation of fibrosis adjacent to the sphincter muscles so that when the track is laid open in the second stage the sphincter will not gape. This period of time can be shortened significantly using the advancement flap technique. Sliding flap advancement also allows the preservation of as much muscle as possible without any risk because division of the contained muscle is not necessary. Therefore sliding flap advancement can be used for the treatment of all types of complicated high level fistulae, even including appropriate cases of extrasphincteric fistulae with a secondary rectal opening and high level anterior fistulae in women[5].

In comparison with the rerouting technique described by Mann and Clifton[2], sliding flap advancement once again has the advantage that for the treatment of high anterior fistulae in women no additional division and suture of the thinned external sphincter or puborectalis is necessary. This may be even more crucial for recurrent high anal fistulae in patients who already have considerable sphincter damage and scar contraction. Oh[6] and Aguilar *et al.*[7], who have also used the sliding flap advancement technique to treat high level fistulae, reported similar good results in terms of preserving sphincter muscles and minimizing functional disturbance. The recurrent rate in the series of Aguilar *et al.*[7] was 1·5 per cent.

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Paper accepted 29 December 1986

Br. J. Surg. 1987, Vol. 74, May, 392–394

New technique for pancreatico-jejunostomy using a biological adhesive

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A new technique of pancreaticojejunostomy using a fibrin glue biological adhesive system (BAS) after pancreaticoduodenectomy is reported. Pancreaticojejunostomy was performed on 112 patients between 1971 and 1985. Forty-two of the patients received BAS application (Group I), but the remaining seventy did not (Group II). To evaluate more precisely the effectiveness of BAS, 22 patients in Group I (Group I–ST) and 26 patients in Group II (Group II–ST) who were operated upon by the same surgeon during the same period were reviewed retrospectively. The selection of patients for the use of BAS was randomized. In Group I–ST, one patient had a minor leak; no major leaks or operative deaths occurred. Two of the twenty-six patients in Group II–ST had minor leaks and one patient had a major leak causing death. This new technique for pancreaticojejunostomy using a biological adhesive system may be useful for preventing anastomotic leaks, especially in a patient with a normal pancreas.

Keywords: Pancreaticojejunostomy, pancreaticoduodenectomy, biological adhesive system, fibrin glue

Although many improvements have been made in operative techniques and postoperative care, pancreaticoduodenectomy remains a technically difficult procedure attended by a relatively high morbidity and mortality associated with pancreatic leaks, especially in patients with a soft pancreas and small main pancreatic duct.

To improve the safety of pancreaticojejunostomy, we devised a new technique using fibrin glue seal as a biological adhesive system (BAS) after pancreaticoduodenectomy and report our clinical experience.

Patients and methods

Pancreaticoduodenectomy was performed on 132 patients with 122 malignant lesions and 10 benign lesions in the First Department of Surgery, Kumamoto University Hospital and affiliated hospitals between 1 January 1966 and 31 December 1985. Three patients with pancreatic cancer underwent ligation of the pancreatic duct after pancreaticoduodenectomy. One hundred and twenty-nine patients had their pancreatic duct reimplanted into the jejunum. Of these 17 patients underwent pancreaticojejunostomy (invaginating type) and the remaining 112 patients had pancreaticojejunostomy (duct-to-jejunal mucosa anastomosis). From October 1978, a new technique of pancreaticojejunostomy, in which a biological adhesive system (BAS) consisting of highly concentrated native fibrinogen, thrombin and clotting factor XIII is applied to the anastomotic region between the pancreatic cut surface and the jejunum, was performed on 42 of 112 patients with pancreaticojejunostomy (Group I). BAS was not used on the remaining 70 patients (Group II).

A profile of the patients and their diseases is shown in *Table 1*.

To evaluate precisely the effectiveness in Group I and Group II, 22 patients (Group I–ST) and 26 patients (Group II–ST) who were operated upon by the same surgeon (S.T.) between October 1978 and December 1985 were compared (*Table 2*). The selection of patients for the use of BAS was carried out at random.

Technique of pancreaticojejunostomy

Pancreaticojejunostomies were by end-to-side anastomosis in all patients. The cut surface of the pancreas was not sutured but haemostasis was performed. The pancreatic duct was freed for a short distance (4–5 mm) and a silicone tube (Fr. 5·5–9·0 according to size of the pancreatic duct) with two side holes was inserted 3–4 cm into the lumen of the pancreatic duct. The duct and the tube were ligated together using 4-0 silk.

A short incision through the seromuscular coat of the jejunum exposed the mucosa in 27 of the 42 patients. The seromuscular layers were not incised in the remaining 15 patients. The first posterior interrupted suture line was placed on the posterior cut surface of the pancreas and the seromuscular coat of the jejunum using 3-0 Surgilon® (black braided nylon, Davis and Geck, Cyanamid Canada Inc., Montreal, Quebec, Canada) with an atraumatic needle. A second layer of posterior sutures was placed between the pancreas and inner jejunal wall using 3-0 Dexon® (polyglycolic acid suture, Davis and Geck, American Cyanamide Co., Pearl River, New York, USA). When the posterior suture lines were completed, a tiny stab incision was made into the jejunal lumen at a point opposite to the pancreatic duct. The pancreatic duct and its stenting tube were inserted into the lumen of the jejunum through the opening and the free end of the tube then brought out through a separate opening in the jejunum. The first anterior suture line was placed on the anterior cut surface of the pancreas and inner jejunal wall using 3-0 Dexon, but the knots tied after application of the BAS. Fresh frozen human fibrinogen, 0·1 g (Fibrinogen-Green Cross, from the Green Cross Co. Ltd, Osaka, Japan) was dissolved in 1·25 ml of distilled water and drawn into a syringe. One thousand JP (Japanese

Table 1 *Patients and diseases for which pancreaticojejunostomy was performed*

	Group I	Group II
Age (years)	61·2 ± 10·6*	59·9 ± 10·5*
Sex M/F	26/16	43/27
Disease		
Cancer of the head of the pancreas	10	15
Cancer of the bile duct	19	20
Cancer of the papilla of Vater	6	19
Cancer of the duodenum	2	5
Cancer of the gallbladder	3	4
Cholangiocarcinoma	0	1
Insuloma of the head of the pancreas	1	0
Papilloma of the papilla of Vater	0	1
Benign structure of the common bile duct	0	1
Chronic pancreatitis	1	3
Pancreatic trauma	0	1
Total	42	70

* Mean ± s.d.

0007–1323/87/050392–03$3.00

Table 2 *Patients and diseases for which pancreaticojejunostomy was performed by the same surgeon (S.T.)*

	Group I–ST	Group II–ST
Age (years)	62·4±8·9	60·3±11.4
Sex M/F	14/8	13/13
Disease		
Cancer of the head of the pancreas	6	3
Cancer of the bile duct	10	9
Cancer of the papilla of Vater	2	7
Cancer of the duodenum	2	1
Cancer of the gallbladder	2	3
Chronic pancreatitis	0	2
Pancreatic trauma	0	1
Total	22	26

Pharmacopoeia) units of thrombin (Thrombin Topical (human)-Green Cross, purchased from the Green Cross Co. Ltd, Osaka, Japan) was dissolved in 5 ml Ringer solution containing 0·2 ml $CaCl_2$ and 1·6 ml of this solution was drawn into a second syringe. Factor XIII (Behringwerke, Hoechst Aktiengesellschaft, FRG) was dissolved in 4 ml of the distilled water and 1·5 ml of this solution was drawn into a third syringe. One millilitre of the fibrinogen solution was applied to the cut surface of the pancreas and the submucosal surface or the serosal surface of the jejunum followed by 1·5 ml thrombin solution and then 1·5 ml factor XIII solution; all were applied to the same area of the anastomosis. The anastomosed area was immediately compressed for 3 min with both hands. The knots on the inside of the anterior suture lines were then ligated and the second anterior suture line was completed. A Penrose drain was placed around the pancreaticojejunal union and a gum drain and Penrose drain were placed in Morrison's pouch.

The technique of pancreaticojejunostomy in Group II was the same except that BAS was not applied. The submucosal surface was used with anastomosis between the pancreas and the jejunum in 62 of the 70 patients. The serosal surface was used in the remaining eight patients.

Minor or major leaks of pancreaticojejunostomy and operative deaths in the two groups were compared. A 'minor leak' at the pancreaticojejunostomy was defined as slight discharge (less than 40 ml) of pancreatic juice from the drain left at the anastomosis or a regional leak of contrast medium at pancreatography which healed with conservative therapy. A 'major leak' was defined as more than 100 ml of discharge of pancreatic juice and bile from the drain left at the anastomosis, or much intra-abdominal bleeding and a leak requiring reoperation or causing death. 'Operative deaths' were considered to be any patients that died before discharge following operative complications.

In vitro *studies of BAS*

If fibrin glue is contaminated with pancreatic juice, rapid fibrinolysis may occur. Therefore we performed studies *in vitro*. Fibrin glue was put in a Petri dish (Clinical Test Ware) containing 20 ml human pancreatic juice taken from four patients undergoing pancreaticoduodenectomy. Furthermore, the effect of local addition of aprotinin (7500–25 000 unit) was investigated.

Statistical analysis

Statistical analysis was performed with the χ^2 test. A probability $\leq 0·05$ was accepted as statistically significant.

Results

Fourteen of the one hundred and thirty-two patients who had pancreaticoduodenectomy died (10·6 per cent). Ten of the fourteen deaths were due to anastomotic leaks between the pancreas and the jejunum.

Five of the seventeen patients who had pancreaticojejunostomy (invaginating type) had leaks from the anastomosis and in three of them death was due to the leak. Anastomotic leaks between the pancreas and the jejunum were the most common cause of postoperative morbidity and mortality.

Three of the forty-two patients in Group I (BAS) had minor leaks and one patient had a major leak and died (*Table 3*). Four of the seventy patients in Group II (without BAS) had minor leaks and six patients had major leaks (*Table 3*). Ten of the seventy patients died (14·3 per cent) (*Table 3*). Pancreatic fistulae were associated with six of these ten operative deaths. The difference between Group I and Group II in major leaks was not significant. However, the major leaks in Group I were three and a half times less frequent than in Group II.

There was a significant difference in operative deaths between Group I and Group II ($P<0·05$).

In Group I, the 11 patients with pancreatic cancer or chronic pancreatitis who had dilated pancreatic ducts secondary to long term obstruction and fibrosis of the pancreas had no leaks and no operative deaths. After exclusion of 11 patients in Group I with pancreatic cancer and chronic pancreatitis, 3 of 31 patients had minor leaks and 1 patient (3·2 per cent) had a major leak. In Group II, only one of the eighteen patients with pancreatic cancer or chronic pancreatitis had a major leak. Four of the remaining fifty-two patients had minor leaks and five patients (9·6 per cent) had major leaks.

One of the twenty-two patients in Group I–ST had a minor leak and none had a major leak or operative death (*Table 4*). Two of the twenty-six patients in Group II–ST had minor leaks and one patient had a major leak and died (*Table 4*).

There was no difference in leak rate between subserosal and serosal anastomoses.

Postoperative pancreatic function depended more on the consistency of the parenchyma of the pancreatic remnant than on the type of anastomosis[1,2]. In many of the patients where the volume ratio of the pancreatic parenchyma was over 70 per cent, the exocrine function (Pancreatic Function Diagnostant (PFD) test, faecal ^{131}I-labelled triolein excretion rate) in the remaining pancreas was good even 3–4 years after pancreaticoduodenectomy. Patency of the pancreatic duct following pancreaticoduodenectomy with pancreaticojejunostomy was examined in seven cases coming to autopsy. The pancreatic parenchyma ratio was more than 70 per cent in five patients (Group I: one patient, Group II: four patients) where the duct was patent, but less than 40 per cent in two other patients (Group I: one patient, Group II: one patient) where the duct was not patent. The pancreatic duct to jejunal mucosal anastomosis was completed and the pancreatic consistency was soft in one patient of Group I whose duct was patent.

In vitro *studies of BAS*

The *in vitro* study showed that the fibrin glue had not dissolved completely even after 48 h without pancreatic juice, but

Table 3 *Anastomotic leaks between the pancreas and the jejunum and operative deaths in 112 patients undergoing pancreaticoduodenectomy*

	Number	Minor leak	Major leak	Total leaks	Operative deaths
Group I	42	3 (7·1)	1 (2·4)	4 (9·5)	1 (2·4)*
Group II	70	4 (5·7)	6 (8·6)	10 (14·3)	10 (14·3)*
Total	112	7 (6·3)	7 (6·3)	14 (12·5)	11 (9·8)

Values in parentheses are percentages
* $P<0·05$

Table 4 *Anastomotic leaks between the pancreas and the jejunum and operative deaths in 48 patients undergoing pancreaticoduodenectomy by same surgeon (S.T.)*

	Number	Minor leak	Major leak	Total leaks	Operative deaths
Group I–ST	22	1 (4·5)	0 (0)	1 (4·5)	0 (0)
Group II–ST	26	2 (7·7)	1 (3·8)	3 (11·5)	1 (3·8)
Total	48	3 (6·3)	1 (2·1)	4 (8·3)	1 (2·1)

Values in parentheses are percentages

when fibrin glue was immersed in pancreatic juice, fibrinolysis occurred after 9·8 ± 3·4 h. Fibrinolysis time was 16·2 ± 4·7 h in the presence of aprotinin.

Discussion

Pancreatic leak due to breakdown of the pancreaticojejunostomy is the most frequent and serious complication of pancreaticoduodenectomy and the most common cause of operative death. Especially when the pancreas has a soft consistency and the main pancreatic duct is small an anastomosis between the pancreatic duct and the mucosa of the jejunum is difficult technically and leaks easily[3]. Therefore a new biogenic tissue adhesive has been used for anastomosis between the pancreas and the jejunum in an attempt to control seepage of pancreatic juice from the transected gland and to strengthen the anastomosis. This system consists of highly concentrated native fibrinogen, thrombin, and clotting factor XIII. The principle of the biological adhesive system is based on the central function of fibrin in blood coagulation and wound repair. It imitates the final step of plasma coagulation at a highly concentrated level. Experimental tissue adhesion was successfully performed in numerous experiments and with various organs[4]. Recently, clinical trials using BAS have been reported in abdominal surgery[4,5], cardiac surgery[6] and orthopaedic surgery[7]. Scheele[3] who used BAS in 118 of 355 patients undergoing extensive abdominal procedures reported that suture line leakage was seven times less frequent than in the control group. We used a biological adhesive system in 42 of 112 patients undergoing pancreaticojejunostomy after pancreaticoduodenectomy. A major leak occurred three and a half times less frequently than in the control group, the difference between Group I (with BAS) and Group II (without BAS) in operative deaths being statistically significant ($P < 0{\cdot}05$).

The present study was not a prospective trial for the purpose of studying the effectiveness of BAS and thus confident conclusions cannot be drawn. However we believe that the material gives valuable information.

The advantages of this method are tissue adhesion, filling up of dead space, control of surface haemorrhage and reduction in seepage of pancreatic juice from the transected gland by sealing the raw surface of the pancreas. When fibrin glue was immersed in pancreatic juice, rapid fibrinolysis occurred *in vitro*. Local addition of aprotinin inhibited rapid fibrinolysis. Scheele[8] reported that the local addition of aprotinin inhibited rapid fibrinolysis and stabilized the adhesive until it was replaced by connective tissue. Aprotinin was not used locally in our clinical study. The reasons for the apparent success of the method are not clear. It may be that the anastomotic region is not immersed in a lot of pancreatic juice clinically. Local application of aprotinin may improve results. A disadvantage of using human fibrinogen and thrombin is the danger of causing serum hepatitis and the appearance of an abnormal immunoreaction, but these problems were not encountered in either Scheele's study[5] or in ours.

The new technique for pancreaticojejunostomy using a biological adhesive system seems to reduce pancreatic leaks, especially when the residual pancreas is normal.

Acknowledgements

We thank Dr Mitsukuni Uchida and Dr Ikuzo Yokoyama for their encouragement, advice and assistance.

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Paper accepted 24 October 1986

Br. J. Surg. 1987, Vol. 74, May, 395–397

Acute pancreatitis associated with carcinoma of the ampulla of Vater

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Acute pancreatitis associated with pancreatic carcinoma or tumour metastases in the pancreas is well documented. In this paper we show a similar association between acute pancreatitis and ampullary carcinoma. Of 41 patients with ampullary carcinoma seen at a single centre over a 25 year period (1959–83), 6 developed acute pancreatitis. Three other patients with a history of obstructive jaundice were noted to show mild transient hyperamylasaemia. Endoscopic retrograde choledochopancreatography is mandatory in the investigation of such patients.

Keywords: Ampullary carcinoma, acute pancreatitis, choledochopancreatography

Acute pancreatitis and metastatic disease involving the pancreas is a rare but well recognized association[1–3], while a similar relationship between acute pancreatitis and pancreatic carcinoma is also well documented[4]. Gambill claims[4] that there is also an association between acute pancreatitis and ampullary carcinoma. However, in his report only one patient out of the nine with ampullary carcinoma appears to have had acute pancreatitis. This case confirms that the two diseases can occur together but does not establish an association between them. Clarke *et al.*[5] report a single patient with familial polyposis, who subsequently developed both an ampullary carcinoma and acute pancreatitis.

We have studied a series of 41 patients with ampullary carcinoma seen at a single centre over a 25 year period (1959–83) and we record the incidence of acute pancreatitis.

Patients and methods

In a retrospective study of 41 patients with a histological diagnosis of ampullary carcinoma 18 had measurement of either serum or urinary amylase (1 patient) concentrations. Six patients had clinical, biochemical and/or operative findings consistent with a diagnosis of acute pancreatitis[6,7], while three more had a history of obstructive jaundice with hyperamylasaemia (normal range below 300 units/l). All six patients with acute pancreatitis presented between 1971–83, three from our own catchment area and three referred from outside it. Prospective studies of acute pancreatitis have been in progress at this hospital since 1971. During the period 1971–83, 770 patients have been admitted with acute pancreatitis[8].

Clinical details of these patients are summarized in *Table 1*. All nine had a history of jaundice and only two patients (7 and 9) had no history of abdominal pain. There was no evidence in any of these nine patients of alcohol abuse. Patients 4, 5 and 7 have been selected to illustrate different clinical presentations and their case histories are described.

Case reports

Patient 4. A 57-year-old woman was admitted as an emergency to a district hospital with a 10-day history of severe upper abdominal pain. Serum amylase concentration on admission was 1800 units/l, confirming the clinical diagnosis of acute pancreatitis. Ultrasound examination revealed a distended gallbladder and gallstones were thought to be present in both the gallbladder and the common bile duct. At laparotomy the gallbladder was distended but there were no gallstones present. The pancreas was hard without evidence of calcification and biopsy of the omentum showed fat necrosis but no tumour.

During the following 3 years she was troubled with recurring abdominal pain and intermittent hyperamylasaemia. At the end of this period she was again admitted as an emergency with severe upper abdominal pain. She was deeply jaundiced and the serum alkaline phosphatase was elevated. Percutaneous transhepatic cholangiography (PTC) revealed a narrowing at the lower end of the common bile duct which was thought to be due to malignancy. There was no evidence of cholelithiasis. Within 24 h of PTC she required laparotomy for biliary peritonitis. The gallbladder was distended and a mass was palpable at the head of the pancreas obstructing the lower end of the common bile duct. Tru-cut biopsy of the pancreas was carried out and a triple bypass performed. Histology of the biopsy showed fibrous tissue but no tumour.

Postoperatively she was transferred to our hospital where endoscopic retrograde cholangiopancreatography (ERCP) was carried out. A well differentiated ampullary carcinoma was noted and confirmed histologically. She had a pancreaticoduodenectomy with pylorus preservation. Following this her blood chemistry returned to normal. The patient is alive and well 4 years after surgery with no recurrence of her abdominal pain or ampullary carcinoma.

Comment: Patient 4 is representative of patients 1–4 (*Table 1*) in whom acute pancreatitis was diagnosed before any biliary surgery. Two of these four patients had cholelithiasis. At initial laparotomy, patient 1 was found to have 'sand'-like material in his gallbladder as well as an ampullary carcinoma. Either finding could account for his episode of acute pancreatitis. Cholecystectomy was performed at his initial laparotomy with local excision of the ampullary carcinoma one month later. Patient 3 had gallstones in his gallbladder. However, in spite of cholecystectomy and negative exploration of the common bile duct he continued to have episodes of pancreatitis for the next 18 months until an ampullary carcinoma was diagnosed and a Whipple's procedure performed.

Patient 5. A 70-year-old man was admitted as an emergency with jaundice, upper abdominal pain radiating through to his back and a history of weight loss (16 kg). Serum amylase measurement was not carried out at this time. An intravenous cholangiogram failed to outline the biliary system. Laparotomy for obstructive jaundice revealed an ampullary carcinoma and a distended biliary system. The tumour was deemed irresectable and cholecystjejunostomy was performed. There was no evidence of cholelithiasis. He was readmitted 23 months later with a similar episode of acute upper abdominal pain radiating to the back. Serum amylase measurement (1950 units/l) confirmed the clinical diagnosis of acute pancreatitis. Gastroenterostomy was performed 2 months later when once again there was no evidence of gallstones. The patient survived a further 20 months.

Comment: Patients 5 and 6 both had laparotomy for painful obstructive jaundice without serum amylase measurement. Both were subsequently shown to have acute pancreatitis. We believe that their first episode of abdominal pain was probably due to acute pancreatitis which was not diagnosed during their initial admission.

Patient 7. A 59-year-old woman was admitted with a one week history of obstructive jaundice, anorexia, nausea and vomiting, and recent weight loss. There was no history of abdominal pain. Blood biochemistry confirmed the clinical diagnosis of obstructive jaundice and the serum amylase was estimated at 320, 500 and 860 units/l on successive days. At subsequent laparotomy for obstructive jaundice an ampullary carcinoma was found and a pancreaticoduodenectomy performed. There was no evidence of cholelithiasis. Thirteen months later she had an episode of acute pancreatitis (serum amylase 5640 units/l) which settled with conservative management. The patient died 22 months later.

0007–1323/87/050395–03$3.00

Table 1 *Details of nine patients with acute pancreatitis or hyperamylasaemia in association with ampullary carcinoma*

	Pre-operative		Surgery				
Patient no.	Serum amylase (units/l)	Diagnosis	Operation	Diagnosis	Postoperative: serum amylase (units/l)	Further surgery, operation	Follow-up (from definitive surgery)
1	12 000	Acute pancreatitis	Cholecystectomy, biopsy ampulla	Cholelithiasis, carcinoma	Not measured	Local excision	Operative death (1 week)
2	Not measured	Obstructive jaundice	Bypass, biopsy lower CBD	Acute pancreatitis, (ascitic fluid amylase 18 600 units/l)	Intermittently elevated	Whipple procedure	Alive (36 months)
3	1152	Acute pancreatitis	Cholecystectomy	Cholelithiasis	Intermittently elevated	Whipple procedure	Alive (12 months)
4	1800	Acute pancreatitis	Laparotomy, biopsy pancreas	No gallstones, pancreatitis	Intermittently elevated	1. Bypass 2. Whipple procedure	Alive (48 months)
5	Not measured	Obstructive jaundice	Bypass, biopsy	Ampullary carcinoma	1950	Laparotomy (inoperable carcinoma)	Died (21 months)
6	Not measured	Obstructive jaundice	Bypass, biopsy	Ampullary carcinoma	Not measured	Whipple procedure—acute pancreatitis at operation and on histology	Died (10 months)
7	500 860	Obstructive jaundice	Whipple procedure	Ampullary carcinoma	5640	—	Died (36 months)
8	Not measured	Obstructive jaundice	Bypass, biopsy	Ampullary carcinoma	430	Whipple procedure	Died (7 months)
9	571	Ampullary carcinoma	Whipple procedure	—	Not measured	—	Alive (30 months)

Comment: Painless jaundice and hyperamylasaemia were noted in patients 7 and 9. The serum amylase concentration was not measured initially in patient 8 who presented with abdominal pain and obstructive jaundice. In the last patient serum amylase measurements immediately after biliary bypass were normal. However, 7 weeks later just before the Whipple resection she was noted to have hyperamylasaemia.

In all nine patients the diagnosis of ampullary carcinoma was finally made either by laparotomy or ERCP. In all five patients treated before 1975 the diagnosis was made at operation, in contrast to the four dealt with since 1981 where the diagnosis was made at the time of ERCP.

Discussion

In our series of 41 patients with ampullary carcinoma, 6 (14·6 per cent) developed acute pancreatitis. While noting the presence of cholelithiasis in 2 patients we believe that the likeliest cause of acute pancreatitis in all 6 patients was their ampullary carcinoma. Therefore, we submit that there is a real association between acute pancreatitis and ampullary carcinoma.

In the 3 patients with mild hyperamylasaemia (7·3 per cent) no cause other than the ampullary neoplasms was found. Although these three patients cannot be regarded as cases of acute pancreatitis, they may represent a lesser degree of pancreatic inflammation associated with ampullary carcinoma. These 3 patients along with the 6 who developed acute pancreatitis account for 22 per cent of the patients with ampullary carcinoma. The 3 patients from our own catchment area with clinical acute pancreatitis also represent 0·4 per cent of patients seen at this hospital (1971–83) with acute pancreatitis. This is a stronger association than that found between acute pancreatitis and hyperparathyroidism in our own[9] and other centres[10]. Since careful prospective studies usually show that more than 80 per cent of patients have acute pancreatitis attributable to gallstones or alcohol abuse[11,12], the association between acute pancreatitis and ampullary cancer represents a rare but important cause of acute pancreatitis.

The importance of recognizing this association is that a potentially curable malignancy may be diagnosed and treated promptly. Unfortunately the presence of gallstones may delay the discovery of the underlying ampullary carcinoma and this emphasizes the importance of careful operative assessment of the biliary tree at the time of cholecystectomy. However, for every patient with idiopathic acute pancreatitis we believe that ERCP is mandatory before surgery. It is also arguable that both serum amylase and lipase measurements and ERCP should be carried out in every patient with idiopathic elevation in serum alkaline phosphatase concentration. In recent years, the diagnosis of ampullary carcinoma in the patients reported in this paper has shifted significantly from an operative to a pre-operative diagnosis made by ERCP and biopsy. This approach is preferable since it allows histological confirmation, pre-operative assessment of the patient and his tumour, and careful pre-operative preparation. Furthermore, in some old and infirm patients treatment by endoscopic sphincterotomy may be the preferred form of management[14,15].

Acknowledgements

We wish to thank the consultant surgeons of Glasgow Royal Infirmary whose patients are reported in this article. We gratefully acknowledge the help of the staff of the Medical Records Department. Thanks are also due to Miss A. Rogerson and Miss L. Gilmour for the manuscript preparation.

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Paper accepted 5 November 1985

Case report

Br. J. Surg. 1987, Vol. 74, May, 397

Seat-belt stomach transection in association with 'Chance' vertebral fracture

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Seat-belt stomach transection is a very rare injury. We report the first known survivor of this injury. The patient had also sustained a 'Chance' vertebral fracture[1].

Case report

A 20-year-old woman was admitted to hospital following involvement in a two car head-on collision. She was a front-seat passenger wearing an inertia-reel lap and shoulder type seat belt. On arrival in the Accident and Emergency Department she was complaining of abdominal pain. Blood pressure was 130/80 mmHg and pulse rate 100 per minute. Abdominal examination revealed bruising across the centre of her abdomen and at the right anterior superior iliac spine. She had generalized tenderness with guarding. While being examined she vomited a large amount of fresh blood. At laparotomy the peritoneal cavity was filled with blood and food debris. The stomach had been completely transected just proximal to the pylorus. No other abdominal injuries were discovered. Gastroduodenal continuity was restored and the peritoneal cavity was copiously irrigated.

On the second postoperative day she complained of back pain. Lateral X-rays of her lumbar spine showed splitting-apart of the neural arch and posterior aspect of the body of the second lumbar vertebra. On the anteroposterior views separation of the transverse and spinous processes was visible (*Figure 1*).

Discussion

Shamblin[2] and Dajee[3] have previously reported seat-belt stomach transection in young adult women, both of whom died from exsanguination. A clinical finding in both cases was central abdominal bruising; the 'seat-belt sign'[4]. If this sign is accompanied by evidence of peritoneal irritation, however minimal, intra-abdominal injuries should be suspected and laparotomy undertaken promptly.

Seat belt injury to the stomach is very rare because of the stomach's relatively protected position. The distal part of the stomach is vulnerable in deceleration, as shearing forces come into play at the 'free–fixed' junction with resultant transection. Alternatively, when the empty stomach is suddenly and forcibly compressed against the vertebral column by a seat belt, vertical transection of the stomach may occur.

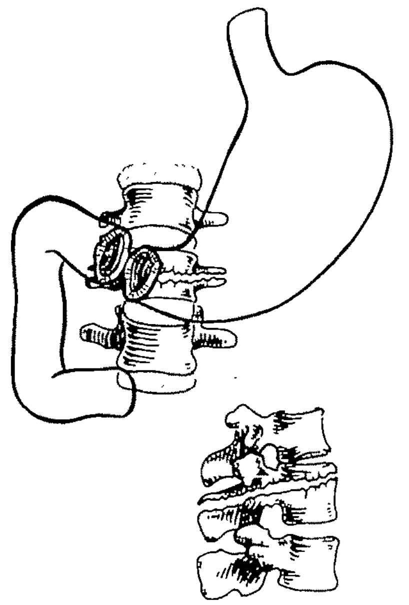

Figure 1 *Diagrammatic representation of seat-belt stomach transection in association with 'Chance' vertebral fracture*

Visceral and vertebral injuries frequently co-exist and one must be wary of falsely attributing signs of reflex ileus to a vertebral fracture in the presence of intra-abdominal injury. The 'Chance' fracture is a true flexion fracture typically seen in high velocity collisions[5]. It is surprisingly stable and after an initial period of bed-rest, a plaster jacket is fitted. The prognosis is excellent.

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Paper accepted 5 November 1986

0007-1323/87/050397-01$3.00

Br. J. Surg. 1987, Vol. 74, May,
398–401

Epidemiology and outcome of acute pancreatitis

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Acute pancreatitis in North-East Scotland from January 1983 to December 1985 was examined. The criteria for diagnosis were a serum amylase > 1000 units/l with a consistent clinical presentation, or acute pancreatitis confirmed at laparotomy or post mortem. All serum amylase assays were performed in one regional laboratory. The commonly used diagnostic coding search for pancreatitis yielded only half the cases found. We identified 378 episodes of acute pancreatitis (196 males and 182 females). The mean annual incidence for first attacks of acute pancreatitis was 242 per million of the population. The commonest aetiology was biliary tract disease (30 per cent of males and 53 per cent of females). Alcohol related pancreatitis occurred in 26·5 per cent of males but only 3 per cent of females. Complications included 26 pseudocysts, 11 pancreatic abscesses, 9 patients with respiratory failure, 11 patients with renal failure and 6 patients with disseminated intravascular coagulation.

Keywords: Pancreatitis, epidemiology

The incidence of acute pancreatitis in reported series ranges from 21·2 to 160 per million of the population[1,2]. The incidence in the Grampian Region of Scotland, UK, has been reported as 104 per million in a retrospective study over an 8 year period[3]. A prospective study for patients admitted to the Aberdeen Hospitals from June 1981 to May 1982 revealed an incidence of 195 per million[4].

Gallbladder disease and alcohol are the main causes of acute pancreatitis although the relative frequency of these aetiological factors varies considerably within the UK and internationally. The present study was undertaken to establish the current incidence of acute pancreatitis in North-East Scotland and in particular to assess any changes in the aetiology or outcome of these cases.

Patients and methods

The case notes of all patients admitted to the Aberdeen Hospitals with acute pancreatitis from January 1983 to December 1985 were studied. The diagnosis of acute pancreatitis was only accepted on the following grounds: a serum amylase concentration > 1000 units/l recorded in the case notes with a consistent clinical presentation; macroscopic evidence of pancreatitis at laparotomy or at post mortem.

The majority were identified by a computer-aided search of all serum samples assayed in the Department of Chemical Pathology, Aberdeen University Medical School, and all patients with a serum amylase > 1000 units/l were reviewed. Serum amylase was measured by the PHADEBAS Amylase Test (Pharmacia)[5]. A computer search of the Scottish Morbidity Record of the international classification of diseases diagnostic index code for acute pancreatitis was also made. Incidence figures are based on the 1984 population data from the Annual Report of the Registrar General of Scotland, for the Grampian Region[6].

Gallstone related disease was based on the identification of cholelithiasis by radiology or ultrasonography. Alcohol related disease was much more difficult to define because of the retrospective nature of the study. This was accepted if, in the absence of other aetiological factors, the patient was clearly documented to take alcohol regularly, or had consumed a large amount of alcohol before admission. Postoperative pancreatitis was diagnosed as a serum amylase > 1000 units/l in patients up to the seventh day after surgery.

Results

We identified 378 episodes of acute pancreatitis in 359 patients in the 3 year period studied. There were 189 male patients (mean age 54·9 years) and 170 female patients (mean age 60·7 years). The annual incidence was 242 per million of the population and was constant in the 3 years analysed.

Laparotomy was performed because of doubt of diagnosis in seven patients. Two had a serum amylase < 1000 units/l and the remainder had a pre-operative serum amylase > 1000 units/l. There were 12 post-mortem examinations performed and in five previously unsuspected pancreatitis was found. Of the biliary related group 73 per cent had a serum amylase concentration > 2000 units/l whereas only 43 per cent of the alcohol related cases had a serum amylase > 2000 units/l.

Aetiological factors

Aetiological factors for each sex are shown in *Figure 1*. Biliary disease accounted for 30 per cent in males and 53 per cent in females whereas alcohol was implicated in 26·5 per cent in males but only 3 per cent in females. The idiopathic group accounted for 19 per cent in males and 22 per cent in females. The proportion of postoperative cases was also equally distributed between the sexes. The number of traumatic cases was small but three times commoner in the male population. There were 26 patients with a variety of probable aetiological factors and these are detailed in *Table 1*. There was no monthly or seasonal variation overall for any aetiological group.

Figure 2 shows the age distribution of the two major aetiological groups. The majority of alcohol related cases occur in males under the age of 60 years with an equal incidence in each decade between 30 and 60 years. Gallstone related pancreatitis is much commoner with advancing age in both sexes though the majority occur in females.

Management of the biliary cases

An ultrasound was performed on 304 patients. Of the 134 patients suffering from gallstone related pancreatitis by ultrasound examination with intact gallbladders, 105 went on to have a biliary operation. One is awaiting operation and one has been referred to a surgeon in another region; 27 had no operation and the reasons for and outcome of conservative management are detailed in *Table 2*. There were 21 patients over 70 years of age; 24 patients had significant concomitant disease and 2 declined surgery. A total of 114 biliary operations were performed and these are shown in *Table 3*. A total of 43 had their biliary operation on their first admission; 33 within 6 weeks (3 of whom had recurrent attacks of pancreatitis whilst awaiting

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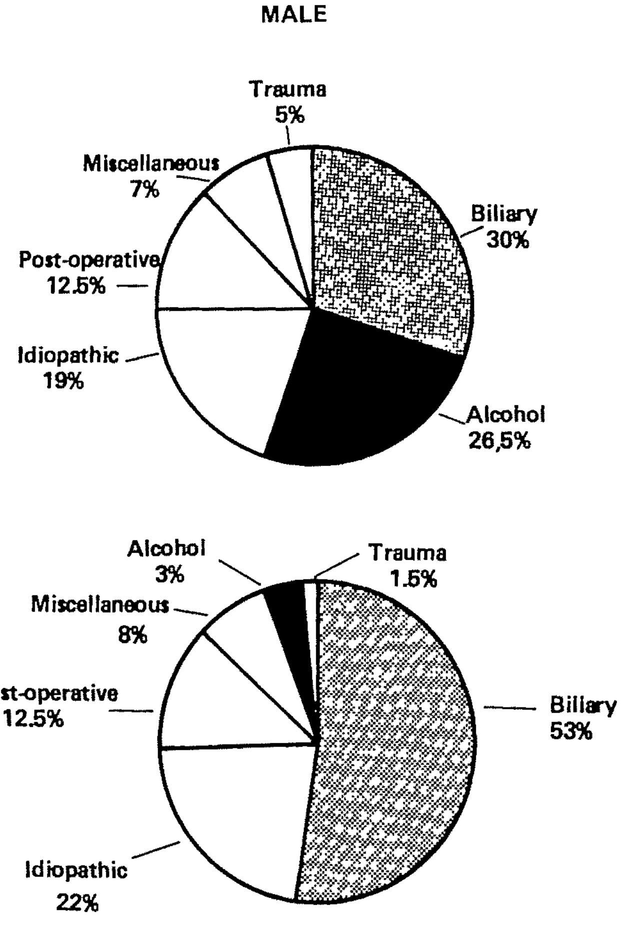

Figure 1 *Acute pancreatitis: aetiological factors (percentage of patients)*

Table 1 *Miscellaneous causes of acute pancreatitis*

Aetiology	*n*
Carcinoma head of pancreas	6
Drugs	7
Hypothermia	3
Viral	4
Sepsis	2
Endoscopic retrograde cholangiopancreatography	4
Total	26

cholecystectomy); 38 had their biliary surgery after 6 weeks (3 of whom suffered from further episodes of pancreatitis before surgery).

Recurrent acute pancreatitis

Table 4 details the aetiology in those with more than one attack of acute pancreatitis in the 3 year period analysed.

Local complications

There were 26 pseudocysts, 18 in males and 8 in females. In males half were alcohol related and only two had biliary disease. In females four were related to gallstones. Eleven were observed and resolved spontaneously and nine were drained internally (eight into the stomach and one into the duodenum). Of the remainder, five were aspirated under ultrasound control and resolved and one was drained externally. There were 11 abscesses (5 males, 6 females). Eight of these were drained externally, one was aspirated, one was internally drained and one was treated conservatively and resolved.

Mortality

In the patients suffering first attacks of pancreatitis 54 deaths occurred giving an overall mortality rate of 15 per cent: 26 patients died of concomitant disease, often after the attack of pancreatitis had resolved, leaving 28 patients who died as a direct result of a complication of acute pancreatitis (pancreatitis related mortality, 7·8 per cent). The average age of those who died was 66·5 years. Mortality related to aetiology is shown in

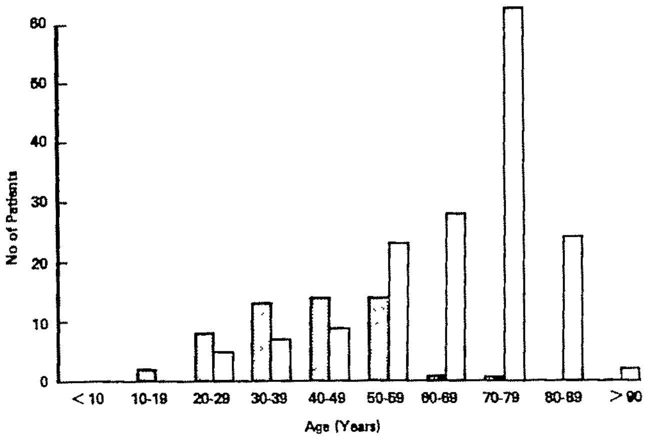

Figure 2 *Age distribution of alcohol □ and biliary □ related cases*

Table 2 *Conservative management of patients with biliary related pancreatitis*

	Age (years)			
	<60	60–69	70–79	>80
n	3	3	9	12
Cardiorespiratory disease	—	2	6	11
Metastatic disease	1	—	1	—
Hepatic failure	2	1	—	—
Declined surgery	—	—	1	1
No surgical referral	—	—	1	—
Mortality				
Pancreatitis related	0	0	0	1
Pancreatitis unrelated	3	0	2	4

Table 3 *Operative treatment of those with biliary tract disease*

Operation	*n*
Cholecystectomy	65
Cholecystectomy + choledochotomy	27
Cholecystectomy + choledochoduodenostomy	13
Choledochoduodenostomy*	4
Choledochotomy*	5
Total	114

* Previous cholecystectomy

Table 4 *Aetiology in patients with recurrent bouts of acute pancreatitis*

	n	
Aetiology	2 Attacks	3 Attacks
Biliary	3	2
Biliary (previous cholecystectomy)	1	0
Alcohol	5	0
Idiopathic	4	1
Total	13	3

Table 5 *Pancreatitis related mortality*

Aetiology	Total	Deaths	%
Biliary	147	11	7·5
Alcohol	55	4	7·3
Idiopathic	73	6	8·2
Postoperative	46	5	10·9
Traumatic	12	1	8·3
Miscellaneous	26	1	3·9

Table 5. Of 26 patients with a pseudocyst 4 died and 5 of 11 with an abscess died. Nine had respiratory failure ($P_{O_2} < 7{\cdot}0$ kPa despite oxygen therapy) and four died. There were 11 patients who developed renal failure of whom 7 died and 6 patients had disseminated intravascular coagulation of whom three died.

Discussion

Comparing the incidence of acute pancreatitis in reported series is difficult because the criteria for diagnosis and methods of case retrieval are either not clearly defined or vary amongst authors. Thus incidences ranging from 21 per million in Nottingham[1] to 160 per million in South-East Scotland[2] may be partly a result of differing approaches to case selection rather than true regional differences.

The first report of acute pancreatitis in the Grampian Region was by Thomson[3]. In a retrospective analysis in the Grampian Region from 1972 to 1979, an annual incidence of 104 per million was reported which exceeded the incidence in comparable English studies. A prospective analysis by the same author[4] of cases presenting to the Aberdeen Hospitals from June 1981 to May 1982 revealed an incidence of 195 per million using the same diagnostic criteria. This highlights clearly the inadequacy of case retrieval using the commonly used computer linked diagnostic index for acute pancreatitis. We have found that this method identified only 53 per cent of our cases. A much more reliable incidence was identified in this study because all serum amylase analyses were performed in one regional laboratory and identification of every patient with a serum amylase >1000 units/l was therefore complete. The only difference from Thomson's prospective study is that we have included seven cases identified at laparotomy or post mortem in the absence of a raised serum amylase. It is unclear therefore why the annual incidence of 242 per million should be so much higher than in the prospective analysis. However this figure accurately represents the current incidence of acute pancreatitis in this region and the rate was constant in each of the 3 years studied. Although there is no proof of an absolute rise in incidence a similar trend has been shown in the Bristol Region. Trapnell[7] and Corfield[8] reported incidences in identical populations of 53·8 and 73 per million for the periods 1950–69 and 1968–79 respectively.

Gallstones and alcohol are the main causative factors but the part played by each in different parts of the world is variable. English studies[1,7,8] have shown a biliary cause in 40–60 per cent which is similar to our findings. Their incidence of alcohol related disease is <8 per cent. This compares with 15 per cent in the present study, 23 per cent in Edinburgh[9] and 26 per cent in Glasgow[10]. In Nebraska, USA[11], alcohol accounts for >40 per cent and in Sweden[12] alcohol related disease has been reported in 68 per cent of cases. People suffering from alcohol dependence are poor witnesses to their own drinking habits. Our finding, that alcohol related pancreatitis is largely a disease of males below the age of 60, is similar to that in Glasgow[10].

As awareness of postoperative pancreatitis is heightened so is its diagnosis and the increasing incidence found in this and other recent studies[4,11,13] reflects this. It may consist of a transient hyperamylasaemia; Morrisey[14] has shown that one third of such cases of transient hyperamylasaemia may be due to a rise of the salivary isoamylase. It may be the most severe form of the disease. In this survey the mortality of postoperative pancreatitis, at 11 per cent, was higher than in any other aetiological group and this correlates with Imrie's[13] and Corfield's[8] findings.

The combined incidence of pseudocysts and abscess at 8·6 per cent is much higher than the 3 per cent found in Thomson's study[3] and is more in keeping with the incidence of 5 and 10 per cent reported by Imrie[10,15]. This must to some extent reflect the increased use of ultrasonography, and to a lesser extent computerized axial tomography, in monitoring patients with signs and symptoms suggestive of local complications. Unlike Thomson's series[3], where external drainage of pseudocysts was more common than cystgastrostomy, only one in the present series had their cyst drained externally.

It is interesting that 25 per cent of those with gallstones on ultrasound had no surgical treatment. The majority of these patients were elderly and were high anaesthetic risks. Although the total mortality in this group was high at 37 per cent, only one patient died as a consequence of a direct complication of acute pancreatitis. The length of follow-up in these cases is short but only one to date has developed a further episode of pancreatitis.

Respiratory failure has been the commonest cause of death in many series[16–18]. This was not so in the present study where 5 of the 9 patients with respiratory failure survived. It is likely that advances in the supportive therapy for this complication have been responsible for the reduction in mortality compared to the earlier study in this region[4] where 18 of 23 patients with respiratory failure died. Renal failure carried a higher risk with a 63 per cent mortality but this is still less than the 80 per cent reported by Imrie[10]. Pancreatic abscess is also a serious complication with a mortality of 46 per cent.

The incidence of pancreatitis in the Grampian Region is high. The current method of case retrieval has yielded an annual incidence of 2·5 times that reported for this region in a previous study[3]. Aetiological patterns however are unchanged with a high proportion of elderly female patients with cholelithiasis and alcohol related disease occurring almost exclusively in males below the age of 60 years.

Acknowledgements

We should like to thank Dr Patterson and the computer staff of the Department of Chemical Pathology, Aberdeen University and Professor Kerridge of the Department of Statistics, Aberdeen University.

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Paper accepted 7 November 1986

Case report

Br. J. Surg. 1987, Vol. 74, May, 401

Response of multicentric desmoid tumours to tamoxifen

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Desmoid tumours are tumours which occur mainly in young women, characteristically in the anterior abdominal wall. Standard treatment is wide surgical excision, but local recurrence rates are high. We report a patient with multicentric desmoid tumours, successfully treated with tamoxifen.

Case report

A 26-year-old woman presented with a 1 cm tender mass in the left breast without lymphadenopathy. Histology of the excision biopsy showed a fibrous lesion with abundant collagen, and mature spindle-shaped fibroblasts. There was no cellular atypia and only scanty mitoses were present. The features were of a desmoid tumour (fibromatosis) and the excision was incomplete. She subsequently developed two further lesions at other sites, one of which recurred following local excision. Histology of each was identical to the original biopsy. At the last operation extensive tumour in the right iliac fossa could not be cleared completely from the iliac crest. She was referred for consideration of local radiotherapy to the tumour bed. However, when seen in the department, she had developed a new 1 cm mass on the abdominal wall. In view of the new lesion as well as bulk disease in the right iliac fossa, it was felt that local radiotherapy would be inappropriate and she was treated systematically with tamoxifen 20 mg daily increasing to 40 mg daily after 1 month. After 2 months of tamoxifen the abdominal wall mass had softened and at 3 months was not palpable. There was no clinical evidence of enlargement of the right iliac fossa tumour. She has remained well on this regime for 14 months, there has been no recurrence of the tumours, and no occurrence at new sites. Apart from menstrual irregularities and slight weight gain, she has experienced no side effects from the tamoxifen.

Discussion

Desmoid tumours arise in musculo-aponeurotic regions presenting as tender swellings. Examination reveals a circumscribed lesion, but histologically there is no capsule formation, and they tend to be locally invasive. They form part of a spectrum of fibrous tissue proliferations, and are intermediate in biological behaviour between benign fibrous lesions and fibrosarcomas. There has been no report of metastasis. They may form part of Gardner's syndrome.

Desmoid tumours are rare but present great management problems. The majority occur in the anterior abdominal wall but they have also been reported in the head and neck, mesentery, pelvis, and breasts. The mainstay of treatment is wide surgical excision, but the recurrence rate is disappointingly high at 45–60 per cent[1,2]. Aggressive surgical treatment (including major amputation) is slightly more successful, but is still associated with a local recurrence rate of 22 per cent[3,4]. Radiotherapy has been advocated with some good responses, but the recurrence rate is still 40–50 per cent, unless > 60 Gy is given over 6 weeks to the tumour bed and very wide margins are used[5,6], when the recurrence rate is 20–30 per cent.

Chemotherapy has been used in juvenile fibromatosis, and for adults with some success using vincristine, adriamycin and cyclophosphamide. Non-steroidal anti-inflammatory drugs, intralesional steroids and ascorbic acid have all been reported in isolated cases. Tamoxifen has been used successfully in three patients with Gardner's syndrome[7,8] although follow-up was short because of concomitant colonic carcinoma. Tamoxifen is widely used for breast cancer. It has a complex structure with known anti-oestrogen effects; however, it also has partial oestrogen agonist effects and direct anti-tumour effects. The mechanism of action in desmoid tumours is unclear. The response of abdominal desmoids to radiotherapy would support the anti-oestrogen theory in that ovarian function is reduced with abdominal treatment. However, neither progesterone or oestrogen receptors have been found in desmoids[9]. Further research is required to fully assess the value of tamoxifen and to determine the ideal length of treatment.

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Paper accepted 21 October 1986

0007–1323/87/050401–01$3.00

Br. J. Surg. 1987, Vol. 74, May,
402–404

Alcohol induced pancreatitis: social and surgical aspects

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During the period 1977–1985, 38 patients with alcohol related pancreatitis (37 men, 1 woman) were referred to a specific pancreatic follow-up clinic; their mean age was 42·4 years (range 20–69 years). At initial presentation 14 patients were unemployed (37 per cent) and 11 worked as unskilled labourers (29 per cent). Twenty-seven patients (71 per cent) required more than one hospital admission. Surgery was indicated in 14 patients (37 per cent): 4 diagnostic laparotomy, 3 cholecystectomy, 3 drainage of pancreatic pseudocyst and 1 pancreatic abscess, 3 biliary bypass and 4 pancreatic resection. Four patients required more than one operative procedure. Five deaths occurred during the study period: one following biliary bypass, one following total pancreatectomy and three not directly related to pancreatitis. Follow-up attendance rates at 1, 3 and 5 years were 76, 47 and 34 per cent respectively. Alcohol induced pancreatitis in Teesside, UK, is a disease of young adult males of lower socio-economic status with a recurring pattern leading to repeated hospital admissions and an unexpectedly high incidence of surgery. The study demonstrates the problem of ascertaining data related to long term follow-up in a condition where, despite intensive efforts, patient compliance is poor.

Keywords: Pancreatitis, epidemiology, alcohol abuse

There is accumulating evidence to suggest that in the UK and elsewhere alcohol abuse is increasing as a primary aetiological factor in pancreatitis[1–4]. Information regarding the natural history of the disease, however, is limited and based mainly on retrospective studies[3–6] with a few notable exceptions[7–9]. In 1974 Olsen reported on a series of 100 consecutive cases of pancreatitis of varying aetiologies with a 1 year follow-up[7] and a prospective epidemiological study of pancreatitis was set up in Copenhagen in 1978[8]. Imrie and colleagues provide long term follow-up for all patients presenting with pancreatitis[9] but follow-up data relating specifically to alcohol induced disease is lacking. A similar pancreatic follow-up clinic was set up in this centre in 1977 and this paper reviews the initial 8 year experience of alcohol related pancreatitis in Teesside, an industrial area in North East England, and emphasizes the social and surgical aspects of the disease.

Patients and methods

Thirty-eight consecutive patients admitted with alcohol induced pancreatitis during the period 1977–1985 were subsequently referred to a designated pancreatic follow-up clinic which was under the supervision of one consultant surgeon (A.L.G.P.). The patients consisted of those referred directly by local general practitioners to the surgeon concerned (A.L.G.P.) together with chronic pancreatitis patients referred by the gastroenterological unit in the hospital. There were 37 men and 1 woman with an age range of 20–69 years (mean 42·4 years).

Pancreatitis was attributed to alcohol abuse in eight patients whose regular intake was >4 pints of beer or ½ bottle of spirits per day[1] and in 30 patients whose regular intake was less but a recent bout of excess drinking (15–25 pints of beer) had preceded admission[2]. In all cases hereditary or drug induced causes of pancreatitis were excluded on history taking, infective and metabolic (hypercalcaemia, hyperlipaemia, diabetes mellitus) causes were excluded by laboratory investigations and gallstone associated pancreatitis was excluded by ultrasound and intravenous cholangiogram studies. None of the patients had had major abdominal trauma or surgery. Pancreatitis was classified as acute or chronic in accordance with the Cambridge modification of the Marseilles classification[10,11].

There were 25 patients who presented with acute pancreatitis, 21 with a typical clinical picture combined with serum amylase >1000 units/l. In four patients with serum amylase <1000 units/l the diagnosis was established at laparotomy. There were 13 patients with evidence of chronic pancreatitis on initial presentation (calcification 7, steatorrhoea 4, recent onset diabetes 2).

Patients were reviewed 6 months after hospital admission and annually thereafter. They were advised of the need for regular follow-up and if they failed to attend they received two further appointments. At review symptoms and details of alcohol intake were recorded.

Results

Socio-economic status

On initial presentation 14 patients were unemployed (37 per cent), 11 were unskilled labourers, 9 were tradesmen, 3 had retired and 1 was a housewife. The type of alcohol consumed was predominantly beer: 32 patients drank beer alone, 5 drank beer and spirits and 1 patient (housewife) drank spirits alone. Excess alcohol intake was associated with cigarette smoking in 29 patients: 5 patients smoked 10–20 per day, 14 smoked 20–30 and 10 smoked >30 cigarettes per day; 2 patients smoked piped tobacco only and 7 patients did not smoke.

Co-existent alcohol related disease

One patient with chronic pancreatitis had clinical and biochemical evidence of chronic liver disease at the time of initial presentation with marginally elevated liver enzymes in the absence of extrahepatic obstruction and decreased serum albumin. A second patient developed cirrhosis 3 years after initial presentation with chronic pancreatitis and subsequently had a portocaval shunt performed. Cirrhosis was confirmed in a third patient at the time of surgery for stricture at the lower end of the common bile duct; this patient died within 30 days of surgery. Five patients required admission for suspected alcohol induced gastritis and three patients were admitted with a combination of alcohol and drug overdose.

Surgery

Fourteen patients (37 per cent) underwent a total of 18 operations related to pancreatitis. Four patients with minor elevation of serum amylase required emergency laparotomy to establish the diagnosis. Cholecystectomy was performed 6–8 weeks later in two of these patients and in a third patient with recent acute pancreatitis where, despite a history of heavy alcohol intake, ultrasound examination had suggested the presence of gallstones; in two of these patients, however, the gallbladder did not contain stones and peroperative cholangiogram was normal. Pain persisted following cholecystectomy in all three and the initial pancreatitis episode was attributed retrospectively to excess alcohol intake.

Seven patients developed a pancreatic pseudocyst. No specific therapy was required in two, two responded to aspiration under ultrasonic control on two and three occasions respectively and the remaining three patients required surgical drainage, one subsequently developing a pancreatic abscess which also required drainage.

Seven patients required surgery for complications of chronic pancreatitis. In three patients bypass surgery was performed for stricture of the distal common bile duct with progressive deterioration in liver function. The benign nature of the stricture was confirmed histologically to be due to chronic pancreatitis: the surgery included cholecystectomy and hepaticojejunostomy-en-Y in one, cholecystojejunostomy and jejunojejunostomy in the second and cholecystectomy and choledochojejunostomy-en-Y in the third patient. The last mentioned later developed a pancreatic pseudocyst which subsequently required surgical drainage. One patient who had undergone surgical drainage of pseudocyst developed a pancreatic abscess 8 months later which was successfully drained externally; this patient then developed diabetes and evidence of exocrine gland failure and eventually underwent total pancreatectomy for persistent chronic pain. Pancreatectomy was carried out for chronic pain in a second patient who also had both endocrine and exocrine pancreatic failure. Two patients with persistent pain and radiological evidence of localized disease (endoscopic retrograde cholangiopancreatography) underwent partial pancreatic resection, one proximal and one distal, with subsequent relief of symptoms.

Mortality and morbidity

Follow-up attendance rates at 1, 3 and 5 years were 76, 47 and 34 per cent respectively and eight patients failed to attend any follow-up (21 per cent). There were two postoperative deaths (within 30 days of surgery) and three patients died during follow-up (overall mortality 13 per cent). One patient (65-years-old) with alcoholic cirrhosis and gross pancreatic ascites died following cholecystojejunostomy for distal common bile duct stricture secondary to chronic pancreatitis and the second was the patient (34-years-old) undergoing total pancreatectomy who had portal vein thrombosis and died due to disseminated intravascular coagulation. Of the remaining three patients, one died of myocardial infarction 3 months following proximal pancreatectomy (58-years-old), the second of mesenteric ischaemia following aortofermoral bypass 4 years after total pancreatectomy (52-years-old) and the third of a cerebrovascular accident (62-years-old) respectively.

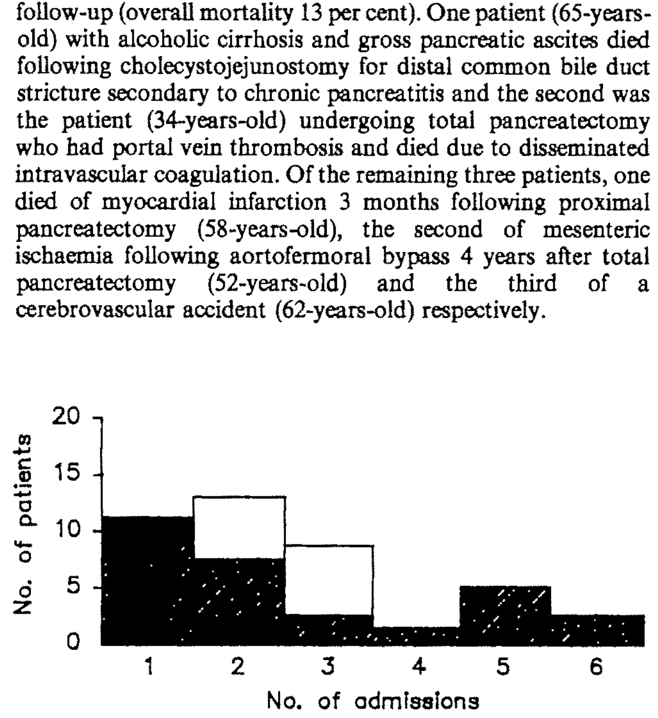

Figure 1 *Pattern of hospital re-admissions.* □, *Elective admissions;* ■, *emergencies*

Table 1 *Indications for re-admission*

	No. of admissions
Emergency	
Relapsing pancreatitis	35
Pseudocyst formation	7
Alcoholic gastritis	5
Drug overdose	3
Unrelated to alcohol	10
Elective	
Re-assessment	8
Surgery	6

There were 27 patients who required more than one hospital admission (71 per cent): 13 required a second, 6 a third and 8 required four or more admissions (*Figure 1*). There were 14 elective re-admissions, the indications being re-assessment due to increasing severity of symptoms (8) and for elective surgery (6) (*Table 1*). In contrast there were 60 emergency re-admissions, the indications being relapsing pancreatitis (35), pseudocyst formation (7), alcoholic gastritis (5) and drug overdose (3). Ten admissions were unrelated to alcohol ingestion or pancreatitis, notably complications related to atherosclerosis in five patients.

Of 28 patients attending follow-up, 7 claimed to have abstained completely from further alcohol intake since their initial hospital admission for pancreatitis. Two of the seven subsequently developed a single relapse while five remained symptom free thereafter. Twenty-one patients continued to drink: five patients who presented initially with acute pancreatitis had no further episodes requiring re-admission, but 16 patients required a total of 33 re-admissions for relapsing pancreatitis, 7 re-admissions because of pseudocyst formation, 5 for alcohol induced gastritis and 3 for a combination of alcohol and analgesic drug overdose. Of these 16 patients, 11 required regular analgesia (Co-proxamol 4, Pentazocine 2 and slow release morphine 5).

Discussion

The results of this study suggest that in Teesside alcohol related pancreatitis is primarily a disease of young beer drinking adult males of low socio-economic status whose drinking pattern is typically episodic. In this study where a particular effort was made to determine exact details of the type of alcohol consumed the emergence of beer as the commonest cause of alcohol induced pancreatitis was indeed surprising. Similar trends have been reported, however, in other areas of the British Isles, particularly in Scotland[2,12]. In contrast the typical patient encountered in other European countries has a history of prolonged regular daily alcohol intake, predominantly wine and spirits, and is from less deprived socio-economic circumstances[5,3,15].

The relationship of episodic 'bout drinking' to attacks of pancreatitis is controversial[2,13]. While bouts of heavy drinking are not always associated with an attack of pancreatitis patients in this study who were not consistently heavy drinkers were known to have had a recent bout of excessive drinking before presentation. Furthermore, almost two-thirds of patients in this study smoked >20 cigarettes per day (63 per cent). Geokas has suggested that the combination of alcohol intake and cigarette smoking because of a common metabolite, acetaldehyde, which is toxic to the pancreas, may have a cumulative detrimental effect[15].

Problems in diagnosis (four diagnostic laparotomies) and misdiagnosis (two cholecystectomies) contributed to the unexpectedly high incidence of surgery in this study group. These excluded, however, the incidence was still remarkable and five patients required a second operation. The referral pattern from the gastroenterology unit within the hospital is such that all surgery performed for chronic pancreatitis in this hospital during the specified study period is likely to have been included in this study.

Mortality directly related to the disease itself is low in this and other series[8] and in our experience patients with alcohol related pancreatitis are more likely to die from other causes, notably atherosclerosis. Morbidity, however, is considerable with 27 of 38 patients requiring a total of 85 further hospital admissions, 75 of which were associated with high alcohol intake. Attempts to motivate patients to abstain from alcohol were only moderately successful (25 per cent of patients) but the potential benefits to these patients in terms of reduction of further episodes of relapsing pancreatitis is highlighted by the results of this study.

This clinic has, therefore, brought to light important features of alcohol related pancreatitis in North East England. In our experience a high proportion of patients defaulted and the success rate in achieving abstinence from alcohol was very low. We feel, therefore, that it is difficult to justify the cost of a follow-up clinic specifically for management of patients with alcohol induced pancreatitis. It would seem that those patients who subsequently abstained from alcohol were sufficiently motivated to do so at the time of hospital discharge. For those who do not the future is likely to be one of repeated hospital admissions and surgery which, combined with the fact that many of these patients are already state dependent because of unemployment, has considerable social and economic implications.

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Paper accepted 11 November 1986

Br. J. Surg. 1987, Vol. 74, May,
405–407

Value of the P_3 amylase fraction as an indicator of the long-term prognosis of acute pancreatitis

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The value of the serum P_3 amylase fraction in the prediction of the course of acute pancreatitis (AP) after the initial episode was studied prospectively. Eighty-eight patients with AP were included. Amylase, lipase, trypsin and the P_3 amylase fraction were measured in serum obtained at the time of discharge. Patients were followed for 60 days after discharge and divided into two groups: 75 patients who did not have complications, of whom 22·6 per cent displayed elevation of one or more pancreatic enzymes at discharge (17·3 per cent hypertrypsinaemia, 9·3 per cent hyperlipasaemia and 6·6 per cent P_3 fraction); and 13 patients who had an unsatisfactory outcome (4 died, 4 developed a pseudocyst and 5 presented with recurrent pancreatitis). All of the latter group had an increase in at least one enzyme at the time of discharge (92·3 per cent P_3 fraction, 69·2 per cent trypsin, 15·3 per cent lipase, and 7·6 per cent amylase). Both the persistence of the P_3 fraction and hypertrypsinaemia were significantly more frequent in patients with an unfavourable outcome than in those with an uncomplicated course ($P<0{\cdot}001$). On the other hand, persistent elevation of total amylase and lipase were unrelated to outcome. The hospitalization time was similar in both groups (good outcome $21{\cdot}4 \pm 1{\cdot}9$ days, unfavourable outcome $17{\cdot}3 \pm 5{\cdot}3$ days). It is concluded that the presence of P_3 amylase fraction or hypertrypsinaemia at the time of discharge from hospital in a patient with acute pancreatitis suggests a risk of a later complication. Careful surveillance until enzyme levels become normal is urged. It is suggested that isoamylase P_3 determination is the most sensitive assay to screen for the complications of acute pancreatitis.

Keywords: Isoamylase, acute pancreatitis, lipase, trypsin, pseudocyst

Acute pancreatitis (AP) can have an unfavourable outcome in a significant number of cases. Mortality may exceed 55 per cent in fulminant forms[1]. On the other hand, the global incidence of pseudocysts is not exactly known, since it depends on the reliability of techniques used for detection (4–7·7 per cent false negatives)[2,3] and on the time lapse between the onset of symptoms and the demonstration of the morphological abnormality[4]. In some patients (12 per cent) who have experienced an episode of AP, the disease recurs if the cause has not been treated, doing so within 6 months of the initial episode in half the patients[5].

It seems logical, therefore, to examine analytical data that may help to predict the possibility of relapse or the development of complications in a given patient. Collins *et al.*[6] noted that measurement of the isoamylase P_3 index in the serum of patients who had suffered an episode of AP might be useful. Their hypothesis was based on the recurrence of AP in one patient and the appearance of a pseudocyst in three others in whom the isoamylase P_3 index at discharge from hospital was

490 ng/ml[7,8] (upper normal limit, mean +2 s.d. in our laboratory) and confirmation from pancreatic sonogram (45 patients), computerized tomography (29 patients) or laparotomy (14 patients)[9]. Other causes of acute abdomen were excluded in all patients. Of the 88 patients, 43 were thought to have gallstone pancreatitis, 26 alcoholic pancreatitis, 10 idiopathic pancreatitis, and 9 miscellaneous causes. Six patients had severe AP and the others had mild or moderate AP according to objective criteria[10]. At the time of admission and before death or discharge 10 ml of blood was drawn from each patient. The patients were followed up by telephone contact or in the out-patient department for 60 days.

Serum was stored at −20°C until assay which was performed within 30 days of venepuncture. Amylase was assayed using a kinetic method with a maltotetraose substrate (Enzym Amy-K, General Diagnostics; mean ± s.d. = 147·3 ± 35 units/l; interassay variation coefficient 2·5 per cent and intra-assay coefficient 0·8 per cent in our laboratory); lipase, by a nephelometric method in a triglyceride suspension (Nephelopacklipasa , Menarini : mean ± s.d. = 37·5 ± 12·3 units / l; interassay variation coefficient 3·2 per cent and intra-assay coefficient 2·1 per cent); trypsin, by RIA (Ria-Gnost Trypsin, Behring Institute: mean ± s.d. = 284·8 ± 102·9 ng/ml; interassay variation coefficient 8·2

[redacted]

Table 1 *Percentage of patients with elevation of different enzymes according to outcome*

	Unfavourable outcome ($n=13$)	P	Good outcome ($n=75$)
Amylase	7·6	n.s.*	0
Lipase	15·6	n.s.*	9·3
P_3	92·3	0·001*	6·6
Trypsin	69·2	0·001	17·3

Results in percentages; *Fisher's exact test

Table 2 *Number of patients with raised enzyme levels, according to the cause of unfavourable outcome*

	Death ($n=4$)	Pseudocyst ($n=4$)	AP recurrence ($n=5$)
Amylase	1	0	0
Lipase	0	1	1
P_3	4	3	5
Trypsin	2	4	3

AP, acute pancreatitis

80 units/l respectively, and P_3 isoamylase was classified as present or absent[11,13].

At the time of admission, 58 per cent (51/88) of the patients studied had increased amylase levels, 82 per cent (72/88) had hyperlipasaemia, and 83 per cent (73/88) displayed a P_3 fraction. Hyperamylasaemia was significantly less common than hyperlipasaemia and presence of the P_3 fraction ($P<0\cdot001$).

At discharge, 34 per cent (30/88) of the patients presented elevation of one of the enzymes or presence of P_3. In 22 (25 per cent), high trypsin concentrations persisted, 17 (19 per cent) continued to show evidence of the P_3 fraction, 9 (10 per cent) had hyperlipasaemia and 1 (1·1 per cent) hyperamylasaemia. Increased trypsin appeared in a significantly greater number of patients than did hyperlipasaemia ($P<0\cdot025$) and hyperamylasaemia ($P<0\cdot001$), but the P_3 fraction was only present in a significantly greater number of patients in comparison with hyperamylasaemia ($P<0\cdot001$), showing no difference with respect to elevated trypsin or lipase levels.

On the basis of the progress of the patients from admission to 60 days after discharge, they were divided into two groups. One group consisted of 75 patients who progressed favourably and did not develop complications. Of these, 23 per cent had at the time of discharge elevation of one or more enzymes in serum (17 per cent trypsin, 9 per cent lipase and 7 per cent P_3) (*Table 1*).

The second group included 13 patients who had an unfavourable clinical course. Four of them died during the initial hospitalization, another four developed a pseudocyst (two after discharge) and five had to be readmitted for recurrence of AP, due to gallstones in four patients and to alcohol in the fifth. The five recurrences and the two patients who developed a pseudocyst after discharge had been clinically asymptomatic and there were no clinical findings to suggest that complications would appear later. All the patients in this group had an abnormality of at least one enzyme ($P<0\cdot001$, with respect to the group which recovered well); 92 per cent had P_3 fraction, 69 per cent hypertrypsinaemia, 15 per cent elevated lipasaemia and 8 per cent hyperamylasaemia (*Table 1*). The distribution of the enzyme elevations present at discharge according to the complications that later appeared is shown in *Table 2*.

Figure 1 shows the mean enzyme values at admission and discharge (or death) in the complicated and uncomplicated groups of patients. The only significant differences were in the isoamylase P_3 levels at the time of discharge or death, which were higher in the group with the unfavourable outcome ($P<0\cdot05$).

Discussion

The present study was designed to evaluate the role of enzyme assays in predicting the course of AP and, in particular, detecting late complications. Serum amylase, lipase, trypsin and P_3 isoamylase fraction were measured on admission and at discharge in 88 patients with AP, of whom 13 (15 per cent) had an unfavourable outcome. According to the results of our study, the enzyme changes that may help to predict the course that the patients will follow are the presence of the P_3 isoamylase fraction at the time of discharge (positive in 92 per cent of the patients who developed complications, as compared with only 6·6 per cent of those who did not present complications, $P<0\cdot001$) and the persistence of hypertrypsinaemia (69 per cent compared with 17 per cent, $P<0\cdot001$). There were no significant differences in serum amylase and lipase concentrations between the two groups.

Hyperamylasaemia persisted at the time of release in only one patient, which could be due to the rather low number of patients who presented with elevated amylase on admission (58 per cent). This circumstance may be accounted for by the lower incidence of hyperamylasaemia in patients with AP of alcoholic aetiology[14]. In our series, hyperamylasaemia was present in 39 per cent of patients with alcoholic AP, while in AP due to other causes it reached 77 per cent.

According to Leclerc and Forest[15], the persistence of elevated amylasaemia, lipasaemia and especially the presence of

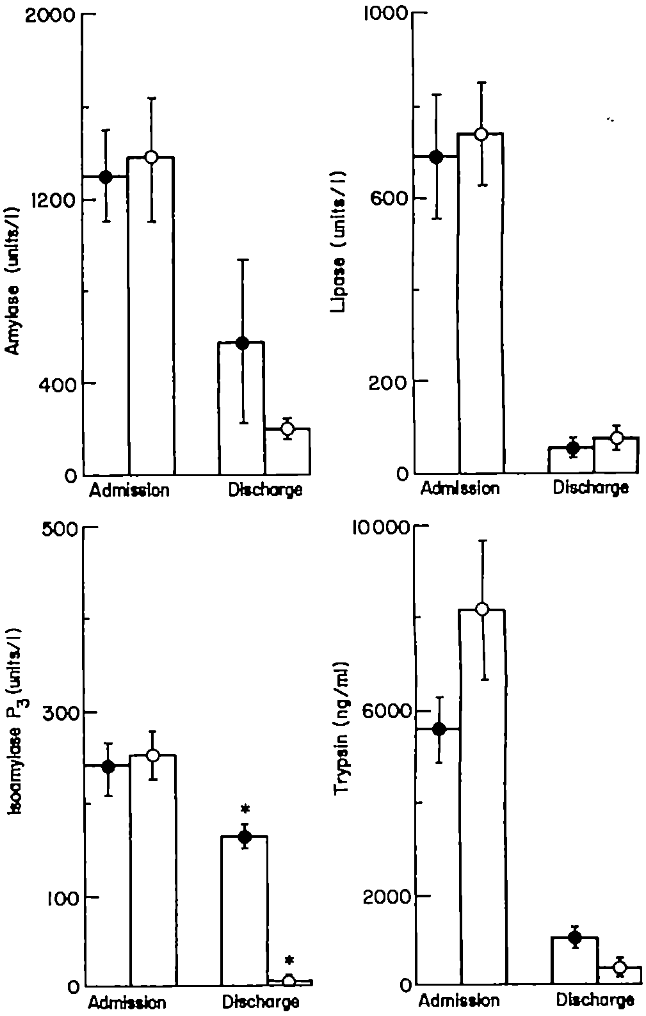

Figure 1 *Mean enzyme values ±s.e.m. presented by patients on admission and discharge, according to whether outcome was good* (○) *or poor* (●); *(P<0·05)

the P_3 amylase fraction do not usually last more than 8 days after the onset of clinical pancreatitis. We found that the mean time from diagnosis to the last enzyme determination in serum at the time of discharge was 21·4±1·9 days (±s.e.m.) in the group that progressed satisfactorily and 17·3±5·3 days in the group which had complications. The time was somewhat shorter in the latter group, although not significantly, because the patients who died were hospitalized an average of 13·5±5·6 days. The patients who progressed favourably, the five who later presented AP recurrence and the four who developed a pseudocyst were discharged when they were completely asymptomatic. Only two patients were known to have small pseudocysts when they left the hospital. Both pseudocysts increased in size and pseudocystogastrostomy was performed. In these two cases, the elevation in trypsinaemia and the P_3 fraction at the time of discharge could be attributed to persistence of an inflammatory pancreatic process. However, in the five recurrences and two undetected pseudocysts, there were no clinical or analytical indications at discharge that suggested persistence of inflammation. The only data were the serum elevations of the P_3 isoamylase and trypsin.

In conclusion, the presence of P_3 amylase fraction or hypertrypsinaemia at the time of discharge in the patients with AP suggests a risk of a later complication. Careful surveillance until enzyme levels become normal is urged. It is suggested that isoamylase P_3 determination is the most sensitive assay to screen for occult complications of acute pancreatitis.

Acknowledgements

The authors are grateful to C. Lopez Rigau for preparation of the manuscript.

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Paper accepted 12 December 1986

Br. J. Surg. 1987, Vol. 74, May,
408–410

Prediction of postoperative pulmonary complications in oesophagogastric cancer surgery

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In a series of 102 patients with cancer of the oesophagus or gastric cardia in whom surgery had been performed, postoperative respiratory infection, respiratory failure and mortality secondary to respiratory complication occurred in 55·8, 34·3 and 21·6 per cent respectively. The incidence of complications correlated well with the pre-operative peak expiratory flow rate when it was <65 per cent of the predicted normal value. However, the predictive ability of peak expiratory flow rate was much less than the patient's age, pre-operative serum albumin level, pre-operative P_{a,O_2} *and number of surgical wounds when all risk factors were considered. Significantly more complications occurred when the patient was >65 years old,* P_{a,O_2} *was <10 kPa, serum albumin was <39 g/l and when the operation required three incisions. These findings may serve as guidelines for identification of high-risk patients in the future.*

Keywords: Pulmonary complications, oesophageal cancer, gastric cancer

Pulmonary complications continue to be a major cause of morbidity and mortality after surgery for carcinoma of oesophagus and gastric cardia[1]. As a majority of the patients are elderly and thoracotomy is often indicated, pre-operative pulmonary assessment is an integral part of management aimed at the identification of high-risk patients. Much is known about the value of pre-operative pulmonary evaluation in pulmonary surgery[2], yet little is known about the correlation between oesophageal surgery and pre-operative pulmonary assessment. We therefore performed a retrospective study to investigate the following problems: (1) is pre-operative pulmonary assessment of value in predicting postoperative pulmonary complications; (2) which parameters in the pre-operative assessment can predict the postoperative pulmonary complications?

Patients and methods

One hundred and fifteen patients with carcinoma of the oesophagus or gastric cardia were seen between June 1979 and May 1986. Of these patients 107 were treated by surgery. Five of these did not have pre-operative spirometry performed. Thus this series comprised 102 patients who had complete data for analysis. Eighty-eight suffered from oesophageal cancer while 14 had carcinoma of cardia.

Pre-operative pulmonary assessment included chest radiography, sputum culture, measurement of arterial blood gases (P_{a,O_2}, P_{a,CO_2} while breathing room air), and spirometry. All patients were given chest physiotherapy and those with radiological and/or bacteriological evidence of pulmonary infection were treated with an antibiotic.

Postoperatively all patients received chest physiotherapy and regular intramuscular pethidine injections. Twenty-three patients (22·5 per cent) who were judged by the anaesthetists to be 'high risk' had postoperative ventilatory support.

Spirometry was performed in the respiratory function laboratory. A Godart Pulmotest spirometer was used before March 1983, after which a Gould 5000 IV computerized pulmonary function system was employed. The following measurements were made:

(1) forced vital capacity (FVC)
(2) forced expiratory volume in 1 s (FEV_1)
(3) ratio of FEV_1 to FVC (FEV_1/FVC)
(4) forced expiratory flow at 50 per cent of FVC (FEF50%)
(5) forced expiratory flow at 75 per cent of FVC (FEF75%)
(6) peak expiratory flow (PEF).

The test was performed with the patient sitting upright. It was repeated three times and the highest value was recorded. The data of Da Costa[3] and Knudson *et al.*[4] were used as reference for normal values.

In the analysis of risk factors, we included other non-pulmonary factors that could possibly influence the occurrence of postoperative pulmonary complications. These included patients' age, need for thoracotomy in the surgical procedure, number of surgical incisions, pre-operative serum albumin level and histological staging of tumour (based on TNM system devised by the Japanese Society of Oesophageal Diseases[5] and Kajitani[6]). Information on smoking habit was available in only 63 per cent of cases. As spirometry can reflect pulmonary changes resulting from smoking, smoking habit was not included as one of the risk factors in this analysis.

We stratified the postoperative pulmonary complications according to the severity as follows:

(1) Respiratory infection. This existed when a febrile episode was accompanied by radiological evidence of bronchopneumonia and/or positive bacteriological sputum culture.
(2) Respiratory failure. This occurred when the patient was unable to maintain P_{a,O_2}>8 kPa and P_{a,CO_2}<7·4 kPa, thus requiring endotracheal intubation, tracheostomy and ventilatory support.
(3) Respiratory mortality. This existed when the patient's death was accounted for solely by the respiratory complications which occurred within the same hospital admission as the operation. Mortality secondary to anastomotic leakage, postoperative haemorrhage or cachexia due to cancer was excluded.
(4) Atelectasis. Minor atelectasis was often difficult to differentiate from respiratory infection, hence for analysis, they were both grouped together as respiratory infection. Major lung collapse required bronchoscopic toilet and ventilatory support afterwards. This complication was grouped under respiratory failure for the purpose of analysis.

Computer-based stepwise regression analysis was employed to determine which of the pulmonary and non-pulmonary factors were significant in predicting the incidence of postoperative pulmonary complications. A separate stepwise regression analysis was performed to select the most significant of the six measurements in spirometry. χ^2 test was used to establish the significance of the proportion of patients having complications postoperatively, whose predictor values were above or below certain levels.

Results

One hundred and two patients' records were analysed. The mean age was 63·6 years (range 41–84 years) and male to female ratio 7·5:1. All patients except two had major procedures (*Table 1*). Respiratory infection occurred in 57 patients (55·8 per cent). Respiratory failure occurred in 35 patients (34·3 per cent). Twenty-two patients (21·6 per cent) died of

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pulmonary complications. Eight patients died of other causes, giving a hospital mortality of 29·4 per cent.

Stepwise regression of the spirometry parameters demonstrated that PEF was the only useful factor in predicting all three categories of pulmonary complications (*Table 2*). Significantly more complications occurred when the PEF was <65 per cent of the predicted normal value (*Table 3*). However, when all the other risk factors were analysed together with the spirometry parameters, PEF was not significant. Instead, patient's age, pre-operative serum albumin, pre-operative P_{a,O_2} and number of wounds became significant factors (*Table 2*). The respiratory failure and mortality rate were raised when the serum albumin was <39 g/l, P_{a,O_2} < 10 kPa and patient's age >65 years. The incidence of respiratory infection was definitely related to the number of wounds, and was higher when the serum albumin was <41 g/l and P_{a,O_2} < 10 kPa (*Table 3*).

The incidence of postoperative pulmonary complications was not influenced by the pre-operative chest infection, pre-operative chest physiotherapy and histological staging of tumour (*Table 4*). The effect of different operations on the complication rate was difficult to assess as the number of patients having each operation was limited. The major difference among these various procedures was whether thoracotomy had been performed. This factor, however, was not significant. Only 22·5 per cent of patients received immediate postoperative ventilatory support. There was no statistically significant reduction in respiratory mortality in this small group.

Table 1 *Types of operation*

Types	Number
Pharyngo-laryngo-oesophagectomy	3
Oesophagectomy via median sternotomy	2
Three-phase oesophagectomy	32
Lewis–Tanner operation	17
Transhiatal oesophagectomy	8
Oesophagectomy via left thoracotomy	3
Oesophagogastrectomy	11
Kirschner operation	17
Bypass by transposed colon	5
Oesophagogastric bypass	1
Thoracotomy and gastrostomy	1
Laparotomy only	2

Since pulmonary embolism may present clinically as postoperative atelectasis, such a condition was particularly looked for in this high-risk group. However, there was no indication, either clinically or from post-mortem examination that this occurred in our patients.

Discussion

Oesophageal cancer surgery carries a high mortality especially when the patients are elderly[7], and when the criteria of selection of patients for surgery are not strict[8]. Of all complications, pulmonary ones are most common. The majority of these patients have pre-existing pulmonary disease, thoracotomy is often required and, in addition, there are unique features in surgery for oesophageal cancer that predispose the patients to pulmonary complications. It has been shown that a combination of a thoracotomy wound with an upper abdominal incision produces a greater disturbance in respiratory function

Table 4 *Histological staging of the tumours*

Stage 0	1
Stage I	6
Stage II	22
Stage III	31
Stage IV	42
Total	102

Table 2 *Significant factors*

Complications	Regression analysis of spirometry parameter only	Regression analysis of all risk factors
Respiratory tract infection (55·8%)	PEF ($t=-3{\cdot}19$, $P<0{\cdot}002$)	P_{a,O_2} ($t=-3{\cdot}17$, $P<0{\cdot}01$) Albumin ($t=-3{\cdot}0$, $P<0{\cdot}01$) No. of wounds ($t=2{\cdot}75$, $P<0{\cdot}01$)
Respiratory failure (34·3%)	PEF ($t=-3{\cdot}60$, $P<0{\cdot}001$)	Albumin ($t=-3{\cdot}25$, $P<0{\cdot}002$) P_{a,O_2} ($t=-2{\cdot}60$, $P<0{\cdot}02$) Age ($t=2{\cdot}42$, $P=0{\cdot}02$)
Respiratory mortality (21·6%)	PEF ($t=-3{\cdot}84$, $P<0{\cdot}001$)	Albumin ($t=-4{\cdot}05$, $P<0{\cdot}001$) P_{a,O_2} ($t=-3{\cdot}03$, $P<0{\cdot}01$) Age ($t=2{\cdot}47$, $P<0{\cdot}02$)

PEF, peak expiratory flow

Table 3 *Cut-off points of significant risk factors*

	PEF		Albumin (g/l) (normal range 45–57)		Age		P_{a,O_2} (kPa) (normal range 10–13)		Number of wounds		
Respiratory infection	<65%	>65%	<41	>41			<10	>10	1 wound	2 wounds	3 wounds
	38 (28)	64 (29)	56 (37)	46 (20)			20 (16)	82 (41)	18 (8)	53 (26)	31 (23)
	$\chi^2=7{\cdot}78$	$P<0{\cdot}01$	$\chi^2=5{\cdot}23$	$P<0{\cdot}05$			$\chi^2=5{\cdot}87$	$P<0{\cdot}05$	$\chi^2=6{\cdot}17$	$P<0{\cdot}05$	
Respiratory failure	<65%	>65%	<39	>39	<67·5	>67·5	<10	>10			
	38 (20)	64 (15)	46 (24)	56 (11)	67 (15)	35 (20)	20 (11)	82 (24)			
	$\chi^2=9{\cdot}02$	$P<0{\cdot}005$	$\chi^2=11{\cdot}86$	$P<0{\cdot}001$	$\chi^2=12{\cdot}32$	$P<0{\cdot}001$	$\chi^2=4{\cdot}72$	$P<0{\cdot}05$			
Respiratory mortality	<65%	>65%	<39	>39	<67·5	>67·5	<10	>10			
	38 (15)	64 (7)	48 (19)	56 (3)	67 (7)	35 (15)	20 (8)	82 (14)			
	$\chi^2=11{\cdot}48$	$P<0{\cdot}001$	$\chi^2=19{\cdot}29$	$P<0{\cdot}001$	$\chi^2=14{\cdot}27$	$P<0{\cdot}001$	$\chi^2=5{\cdot}0$	$P<0{\cdot}005$			

PEF, peak expiratory flow
Figures in parentheses are the number of patients with complication

than either incision alone[9]. An intrathoracic stomach is suggested as the cause of a reduction in FVC as it occupies part of the thoracic cavity[9]. Damage to the diaphragm and vagal nerve appears to be responsible for the inability to cough efficiently[10]. Obviously it is necessary to identify pre-operatively the patients at risk, in order to institute prophylactic measures for those in whom surgery is planned and to offer alternative treatment for those at particular risk. Spirometry therefore becomes an important assessment tool. Data correlating spirometry with postoperative pulmonary complications in patients with pulmonary surgery have been recommended as guidelines for selection of patients[2]. However, as oesophageal cancer surgery differs from lobectomy or pneumonectomy in many aspects, a different set of guidelines is mandatory. Although Sugimachi *et al.*[11] demonstrated that there was no relationship between pre-operative pulmonary function and the incidence of postoperative pulmonary complications, Wong[7], using a much larger population, showed a significantly greater incidence of morbidity in the increased 'respiratory risk' group. Based on the sample size of the present study, we are able to demonstrate, in addition, that PEF was the most important parameter of the six tested in predicting postoperative pulmonary complications. This finding accords well with the studies by Stein *et al.*[12] on a heterogeneous group of patients, and of Gerson[13] on patients with bronchogenic carcinoma.

Other pulmonary and non-pulmonary factors have been considered as significant contributors to postoperative pulmonary complications. As malnutrition is a major problem in oesophageal cancer and it predisposes the patient to infection, we also included the serum albumin level as one of the factors in this analysis. When all the parameters were analysed, the PEF was not significant; while the serum albumin level, patient's age, P_{a,O_2} and number of wounds were found to be important predictor variables.

That the patient's age is an important predictor is not unexpected as the PEF, P_{a,O_2} and the upper airway reflex activity decrease with ageing[2]. Malnutrition as indicated by hypoalbuminaemia is associated with reduced diaphragmatic mass[14], diminished vital capacity, and decreased lung protein synthesis[15]. Its important role in oesophageal surgery is highlighted in this study. Arterial hypoxaemia occurred postoperatively in patients, possibly as a result of intrapulmonary shunting. Bishop and McKeown also demonstrated that P_{a,O_2} fell precipitously to 65 per cent of the pre-operative value on the second postoperative day and the fall was greater when there was a combination of an abdominal and a thoracic wound[9]. These facts support the findings in this analysis.

Identification of a high risk group implies that prophylactic measures must be taken if surgery is planned. Vigorous chest physiotherapy, cessation of smoking and treatment of chest infection are mandatory. Nutritional repletion while waiting for surgery may improve the immune response[16] and muscle function[17]. Postoperatively high-risk patients should be ventilated and the decision to extubate guided by the ability to cough[10]. When the first sign of sputum retention appears, minitracheotomy may help to clear the sputum and interrupt the vicious cycle that may end in respiratory failure and death[18]. There may be a place for modifying the three-phase oesophagectomy to subtotal oesophagectomy via right thoracotomy followed by the stapled anastomosis at the apex of right pleural cavity, thus reducing the number of incisions[19].

In summary, a retrospective study of 102 patients with cancer of the oesophagus or gastric cardia revealed that postoperative pulmonary complications were a serious problem. Simple laboratory data, particularly pre-operative P_{a,O_2} and serum albumin level together with the patient's age, were parameters having a high correlation with pulmonary complications. If spirometry was evaluated alone, PEF was the most important measurement to be considered. These findings may serve as guidelines for identification of high risk patients in the future.

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Paper accepted 5 November 1986

Br. J. Surg. 1987, Vol. 74, May,
411–415

New physiological method of evaluating oesophageal transit

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A method of measurement of oesophageal transit time in the upright posture of a chewed solid bolus has been developed and assessed in normal volunteers (n = *16*) *and in 32 patients with oesophageal disease: organic stricture* (n = *5*), *oesophageal motility disorders* (n = *19*) *and reflux oesophagitis without stricture formation* (n = *8*). *The test involves swallowing a 10 ml poached egg white bolus labelled with* ^{99m}*Tc sodium pertechnetate and external scanning by a gamma camera. An on-line computer program allows detailed analysis by the condensed image technique (which demonstrates the pattern of oesophageal transit) and activity–time curves for the whole, the upper, middle and lower thirds of the oesophagus. The reproducibility of the test is good (coefficient of variation of the total transit of 14 per cent). The results on the normal volunteers have shown that oesophageal transit slows in an aboral direction with transit being faster in the upper, when compared with the middle and lower thirds. The test clearly differentiates patients with oesophageal disease from the normal. The condensed image analysis appears to be useful in outlining the pattern of transit in patients with motility disorders. Patients with reflux oesophagitis have delayed oesophageal transit.*

Keywords: Oesophageal transit, oesophageal motility

Evaluation of oesophageal motility, to date, has been performed under less than physiological conditions. Oesophageal manometry is invasive and usually performed on a fasting subject. Radionuclide transit studies, while non-invasive, are performed using a liquid bolus; thus the subject must be supine to offset the effect of gravity on the liquid.

We have sought to develop a technique which closely reproduces the normal ingestion of solid food while in the upright posture. The resultant technique, a modification of the radionuclide transit test, utilizes a solid bolus, chewed and swallowed by a subject while in the upright position. As an initial evaluation, results in asymptomatic volunteers have been compared to results in patients with known oesophageal disease.

Subjects

Sixteen volunteers (mean age 40 years, range 27–69) without symptoms of dysphagia or gastro-oesophageal reflux and 32 patients (mean age 52, range 24–76) with known oesophageal disease underwent evaluation of oesophageal transit of a solid bolus. This study was approved by the Ethics Committee of the University of Dundee. The patient group included five patients with structural abnormalities of the oesophagus (1 stricture, 2 gastric or jejunal replacement following oesophagogastrectomy, 1 postcardiomyotomy for achalasia, and 1 colonic interposition for congenital short oesophagus), 19 patients with manometrically demonstrable motility disorders and 8 with oesophagitis confirmed by fiberoptic endoscopy, but with normal oesophageal manometry.

To prepare the labelled solid bolus, 150–200 MBq of ^{99m}Tc sodium pertechnetate was added to 5 mg of stannous chloride and incubated at room temperature for 20 min; 0·1 ml of the resultant colloid (15–20 MBq) was then added to 10 ml uncooked egg white and stirred vigorously until mixed. The mixture was then poached to a solid (≈ 4 min).

The subject fasted for 4 h and was then positioned, standing upright, facing a 53 cm field-of-view scintillation camera. The region of the oropharynx and the upper abdomen were included in the field of view. A single static view, taken using a small ^{99m}Tc source, was used to mark the cricoid cartilage. The subject was then instructed to chew the egg white bolus until ready to swallow all 10 ml in one swallow. On a signal, imaging was begun and the subject swallowed the bolus. Repeat dry swallows were then performed every 20 s for the duration of the test. Serial 0·5 s frames were collected for a total of 4 min and stored by an on-line computer.

Analysis of data

The series of dynamic frames were compressed into a parametric 'maximum count image'. This single image was created by the computer stepping through the serial frames and replacing the count in each particular pixel with the count in the same pixel of the next frame only if the value in the second pixel was greater. This image was used to define the body of the oesophagus using the cricoid marker and the gastro-oesophageal junction as landmarks. The body of the oesophagus was then divided into three equal parts for further analysis (*Figure 1*).

Activity *versus* time curves, quantifying the passage of the labelled egg white through the entire oesophagus were then generated (*Figure 2*). Transit time was defined as the time from entry of activity until the time when > 90 per cent of the activity had cleared[1]. In addition, the region of the oropharynx was also evaluated to ensure that the bolus was swallowed entirely during the initial swallow. This evaluation of the input of activity into the proximal oesophagus was crucial in the determination of transit times, especially for the proximal third. To aid interpretation, a condensed image[2,3] was also generated. To create this computer generated image, each consecutive frame of the dynamic study was added side-by-side using a row summation technique. Thus, a single view parametrically describing the entire dynamic sequence was generated (*Figure 3*). This condensed image, with time on the horizontal axis and the vertical axis representing spatial arrangement of the labelled egg white in the oesophagus and stomach, was useful in assessing the pattern of the radionuclide bolus transit through the oesophagus during the entire study.

Results

Transit times obtained in the study of 16 asymptomatic volunteers are listed in *Table 1*. The transit of the radionuclide labelled egg white was significantly faster through the proximal third than through the middle or distal thirds ($P<0\cdot001$, Wilcoxon matched pairs signed test). Likewise the transit through the middle third was significantly faster than transit through the distal third ($P<0\cdot005$, Wilcoxon matched pairs signed test). Six volunteers underwent repeat testing after a 2–3

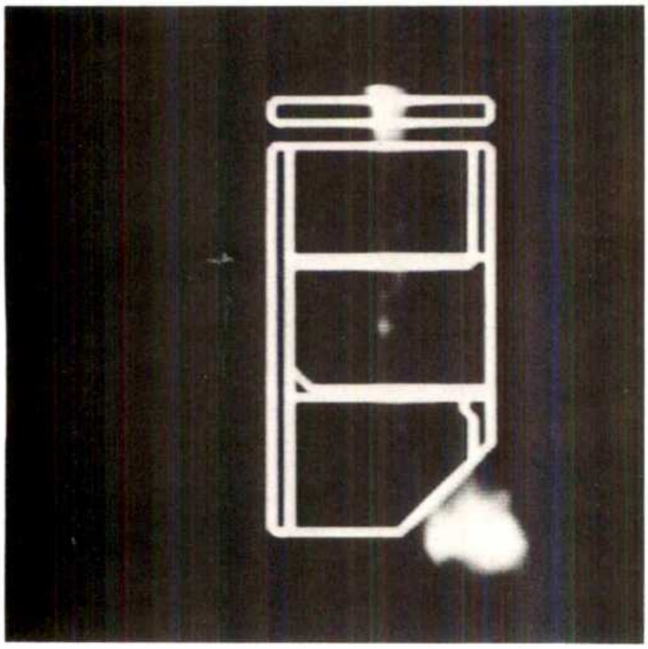

Figure 1 *Maximum count image of an oesophageal egg transit test. Body of the oesophagus has been divided into 3 parts of equal length. The region of the oropharynx is delineated at the top*

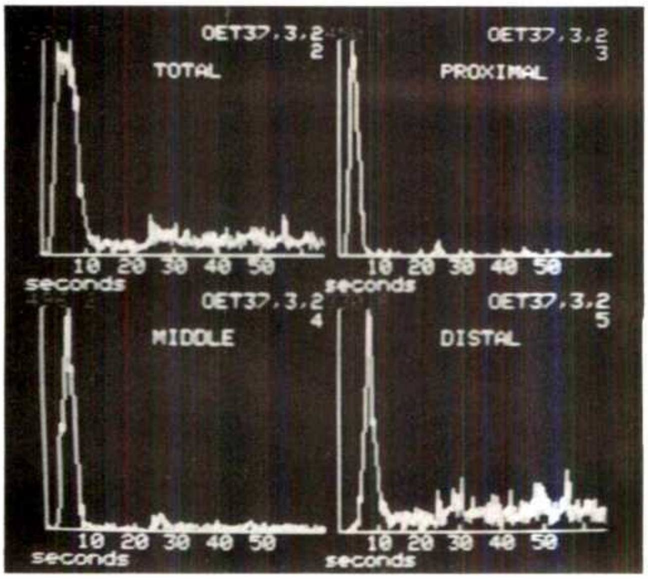

Figure 2 *Activity versus time curves of an oesophageal egg transit test from a normal volunteer for the total oesophagus and constituent thirds. Only the first 50 s of the test are shown*

week interval. The correlation coefficient between the results obtained in the first test and in the second was 0·85 ($P < 0{\cdot}001$). The coefficient of variation for the first and second test was 14 per cent for the total transit time, 12 per cent for the proximal third transit time, 15 per cent for the middle third and 16 per cent for the distal third.

In the five patients with structural abnormalities of the oesophagus, all five failed to clear the bolus in the 250 s test. The oesophageal transit times of 19 patients with oesophageal motility disorders as documented by manometry are listed in *Table 2*. Delay in transit was seen in disorders of decreased motility and in disorders of hypermotility, although patients with only increased wave amplitudes, but normal propagation, have only minimal abnormalities in transit times.

Results in patients with different types of motility disturbances are seen in *Figures 4*, *5* and *6*. With increasing abnormality as demonstrated by manometry, there was a corresponding increased delay seen in oesophageal transit. The pattern seen in the condensed image differed markedly as the motility disorders of the patient became more severe. As the command swallows were performed every 20 s, the effect of each swallow on the passage of the labelled egg white bolus could be demonstrated. In *Figure 4*, which shows a patient (no. 2 in *Table 2*) with poorly propagated wave activity, the bolus is retained most noticeably in the mid-oesophagus, after the first swallow. Ninety per cent of the bolus was cleared at 31 s and complete clearance was achieved at 40 s with the second dry swallow. These patients had periods of normal baseline oesophageal pressure between swallows and exhibited some clearance of the oesophagus with each swallow but achieved total clearance of the bolus only after the fourth dry swallow. *Figure 5a* shows the condensed images of a patient with diffuse oesophageal spasm. There is no clearance with swallows and, by expanding the time axis of *Figure 5* during the first 60 s of the test, the almost rhythmic to and fro motion of the bolus in the oesophagus was clearly demonstrated (*Figure 5b*).

The oscillatory pattern as demonstrated by the condensed image technique appears to be confined to patients with uncoordinated oesophageal muscular activity. Oscillations were noted in the three patients with diffuse oesophageal spasm and in four out of five patients with tertiary contractions. No oscillatory pattern was noted in patients with aperistalsis or with patients demonstrating peristaltic activity on manometry but with changes in wave amplitude and speed of propagation.

The transit times for the eight patients with endoscopically proven oesophagitis are shown in *Table 3*. Delay in transit was seen not only in the distal oesophagus, the site of endoscopic abnormality, but also in the proximal and middle oesophagus as well. It is interesting to note that patients 3, 4, 6, 7, 8 in *Table 3* did not report dysphagia on specific questioning.

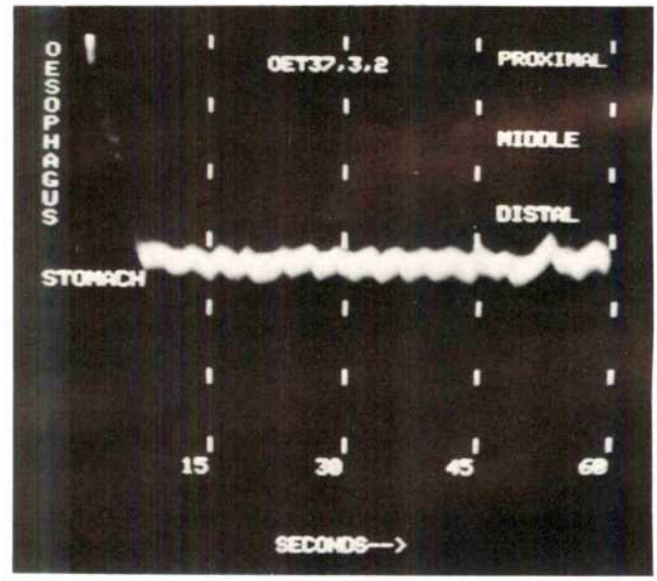

Figure 3 *Condensed image from a normal volunteer. Spatial arrangement of the labelled egg-white in the oesophagus and stomach is on the vertical axis and time is on the horizontal. Only the first 60 s of the test are shown. Note that the bolus descends smoothly through the oesophagus. The image allows qualitative assessment of bolus transit*

Table 1 *Oesophageal transit time in normal volunteers* (n = *16*), *mean ± s.d.*

Segment	Transit time (s)
Total	10·4 ± 1·6
Proximal third	4·7 ± 1·6
Middle third	6·5 ± 1·5
Distal third	0·4 ± 2·5

Table 2 *Oesophageal transit time in patients with known motility disorders defined by manometry*

Patient no.	Manometric data	Transit time (s) Proximal third	Middle third	Distal third	Total	Condensed image oscillatory pattern
1	Aperistalsis	> 250	> 250	> 250	> 250	No
2	Decreased wave propagation	8	29	30	31	No
3	Decreased wave propagation	22	127	127	129	No
4	Decreased wave propagation	14	7	9	20	No
5	Decreased amplitude of wave	15	210	210	217	No
6	Decreased amplitude, decreased propagation	12	15	15	22	No
7	Decreased amplitude, increased duration	5	> 250	> 250	> 250	No
8	Decreased propagation, repetitive activity	27	88	92	92	No
9, 10, 11	Diffuse oesophageal spasm	> 250	> 250	> 250	> 250	Yes
12	Increased amplitude	9	8	9	14	No
13	Increased amplitude	6	8	10	12	No
14	Decreased wave propagation, tertiary contractions	6	> 250	> 250	> 250	Yes
15	Aperistalsis	30	> 250	> 250	> 250	Yes
16	Decreased wave amplitude	5	> 250	> 250	> 250	Yes
17	Decreased wave propagation, decreased amplitude, tertiary contractions	7	> 250	> 250	> 250	Yes
18	Repetitive activity, multiple tertiary contractions, minimal wave propagation	4	> 250	> 250	> 250	No
19	Diffuse tertiary contractions	6	> 250	> 250	> 250	Yes

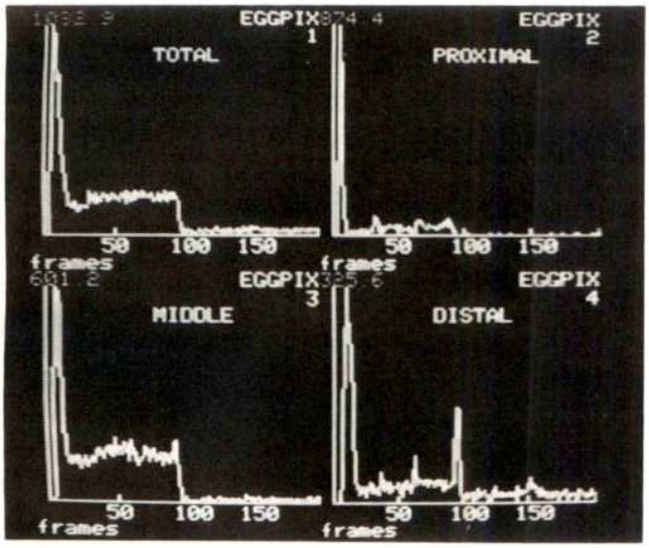

Figure 4 *Activity* versus *time curves from a patient with poor wave propagation on swallowing as assessed by manometry*

Discussion

Dysphagia is a common symptom in patients with oesophageal disorders. Symptoms may be secondary to organic disease, i.e. peptic stricture, a motility disorder, or a combination of the two[4]. Contrast radiography and endoscopy are useful accurate means of detecting and evaluating gross structural abnormalities but have not proved to be successful in the investigation of oesophageal motility disorders[5-7]. Oesophageal manometry has been widely used in the evaluation of oesophageal motility, but this investigation has several drawbacks. Considerable skill is required both in the performance of oesophageal manometry and especially in the interpretation of results[8,9]. Even in expert hands, there is tremendous variation in reported values for normals and in the definition of motility disorders[10,11]. In addition, manometric evaluation is invasive, requiring intubation of the oesophagus, which is unphysiological and is not without patient discomfort[12]. Furthermore, patients are often symptomatic only during ingestion of meals, whereas standard manometric evaluation is performed in the fasting state when these patients are asymptomatic[13]. Attempts to overcome this problem

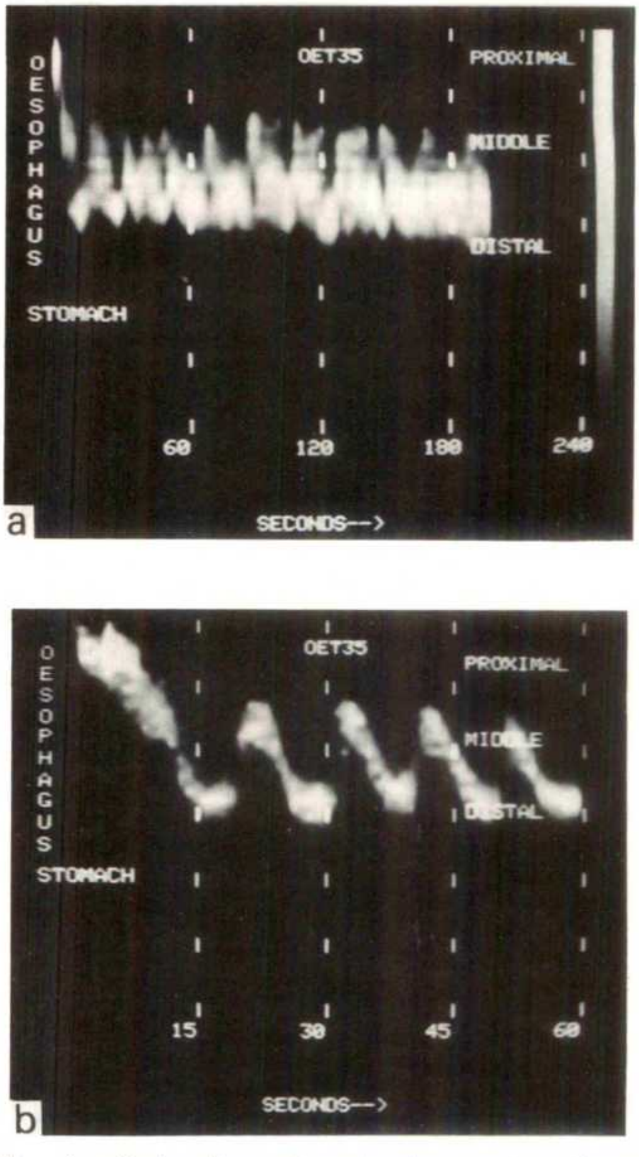

Figure 5 **a** *Condensed image of oesophageal egg transit test from a patient with diffuse oesophageal spasm by manometry.* **b** *First 60 s of* Figure 5a *expanded along the horizontal axis (time)*

Table 3 *Oesophageal transit times in patients with oesophagitis and normal manometry*

Patient	Endoscopic finding	Transit time (s)			
		Proximal third	Middle third	Distal third	Total
1	Grade III	66	82	22 + R	84 + R
2	Grade I	12	110	115	117
3	Grade I	35	36	43	45
4	Grade I	20	84	200	200
5	Grade I	4	45 + R	47 + R	48 + R
6	Grade III	5	33	35	37
7	Grade I	27	6	35	50
8	Grade I	Patient did not swallow entire bolus			

Grade I, erythematous, friable oesophagitis; grade III, linear ulcerative oesophagitis; R, retropulsion of activity

include pharmacological stimulation of the oesophagus[10] or the addition of an ingested meal[14] in conjunction with manometric evaluation.

Kazem[15], in an effort to produce a more physiological method of evaluating oesophageal motility, described the first radionuclide transit studies in 1972. As originally described, the subject swallowed a labelled liquid bolus in the erect posture. However, others have modified the test and generally subjects are studied in the supine posture to offset the effect of gravity on the liquid bolus[1,12]. The detection of hypomotility disorders (i.e. achalasia) has been very good, but the detection of hypermotility disorders has been reported as unsatisfactory (sensitivity < 50 per cent)[16,17] while others have reported good results[18]. We felt the evaluation of oesophageal transit of a liquid in a supine subject to be non-physiological, yet the simplicity and high patient acceptability of radionuclide transit studies are well established.

As dysphagia to solids often precedes dysphagia to liquids, and because ingestion of food can elicit motility disorders and consequent symptoms[13], the use of a labelled solid bolus is a logical choice in the evaluation of oesophageal transit. Previous attempts to label solids have led to elaborate schemes[19], but recent reports have shown the ease and reliability of labelling egg-white, which can then be cooked to a solid consistency, and tests have shown this to be a reliable and stable bolus[20,21].

The use of a solid bolus (4 ml of gelatin labelled with 75 MBq Tc) in the investigation of oesophageal transit has been previously reported[22], but the subjects were studied in the supine posture and the bolus was not chewed before swallowing. We have developed a method that evaluates the subject in the erect posture, swallowing a bolus that has been subjected to normal mastication. This not only reproduces more normal conditions, but it has been shown that posture (erect *versus* supine) has a significant effect on oesophageal peristalsis[23] and therefore it is desirable to imitate the normal physiological situation of upright food ingestion as closely as possible.

We have investigated the use of a solid bolus oesophageal transit study performed with the erect subject. Preliminary results have shown that asymptomatic volunteers can be reliably distinguished from patients with known oesophageal disease. Reproducibility has been good and patient acceptance has been excellent. The use of computer aided analysis has allowed detailed evaluation of oesophageal transit in normals and in patients. The previously described normal aboral slowing of peristalsis[1,12] has been confirmed. Patients with abnormal oesophageal manometry have shown delay in transit of the labelled egg white, although the delay is minimal in patients in whom the only manometric abnormality is increased amplitude of the peristaltic wave.

The detection of an oscillatory pattern in the condensed image appears to be closely associated with uncoordinated oesophageal activity. This may well help to distinguish between motility disorders such as aperistalsis and diffuse oesophageal spasm.

In patients with oesophagitis by endoscopy, we have seen a delay in transit in seven of eight patients studied, in spite of normal manometry. Russell *et al.*[24] have shown that the use of the liquid bolus radionuclide transit study was more sensitive than manometry (39 *versus* 18 per cent) in detecting a motility disorder associated with oesophagitis. Although direct comparison is necessary, it would appear that solid bolus transit, performed in an upright subject may be even more sensitive in detecting a delay in oesophageal transit associated with oesophagitis.

In the one patient who did not swallow the bolus properly, the use of the condensed image allowed qualitative assessment of oesophageal function, although quantitative assessment was impossible. The integrity of the initial swallow must be confirmed in each patient making it mandatory that the region of the oropharynx be included in the field of view.

These preliminary results with the new oesophageal-egg transit test are encouraging and indicate a potential for its use in the evaluation of patients with organic and non-organic dysphagia. A modern Nuclear Medicine Department would require no special equipment and the cost per evaluation is low with minimal radiation to the patient. Further evaluation of this method, including larger numbers of controls and direct comparison with existing methods, is necessary to ascertain the exact place of this investigation in the management of patients with oesophageal motility disorders.

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Paper accepted 15 November 1986

Surgical workshop

Br. J. Surg. 1987, Vol. 74, May, 415

Non-surgical closure of a benign oesophagobronchial fistula

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We describe a case of benign oesophagobronchial fistula, secondary to partial dehiscence of an oesophagojejunal anastomosis, which was closed by the injection of a biological glue, isobutyl-2-cyanoacrylate (Bucrylat, Ethicon).

Case report

A 55-year-old man was operated on for gastric lymphoma. A total gastrectomy with oesophagojejunal Roux-en-Y anastomosis was performed. In the postoperative period a partial dehiscence of the anastomosis occurred and an oesophagobronchial fistula was confirmed by barium swallow (*Figure 1*). Oesophagoscopy showed an orifice 5 mm in diameter. Several biopsies ruled out the presence of malignancy. The patient was treated with aspiration of the oesophagus and total parenteral nutrition but had repeated episodes of pulmonary infection associated with severe respiratory failure, requiring ventilatory assistance.

The poor state of the patient ruled out the possibility of surgical closure of the fistula. As an alternative endoscopic closure[1] was attempted by injecting glue around the oesophageal ostium. Isobutyl-2-cyanoacrylate is a biological glue that has been used to close superficial wounds, for vascular embolization and for pancreatic duct obstruction[2]. It is presented in a liquid form and solidifies immediately on contact with blood or moist substances. Without anaesthesia a fibrogastroscope was passed into the oesophagus until the orifice of the fistula was seen. Using the flexible injection needle used in sclerosis of oesophageal varices, 4 ml of glue was injected into the submucosa around the fistula with the aim of closing the tract without closing off the affected bronchus. Subsequently the lumen of the fistula was injected with an additional 2 ml of glue.

Recovery was uneventful. The patient was supported by total parenteral nutrition without oesophageal aspiration. After 2 weeks a barium swallow confirmed the complete closure of the fistula (*Figure 2*). The patient reassumed oral feeding without problems and was discharged in good health a short time thereafter. At 8 months follow-up he was asymptomatic.

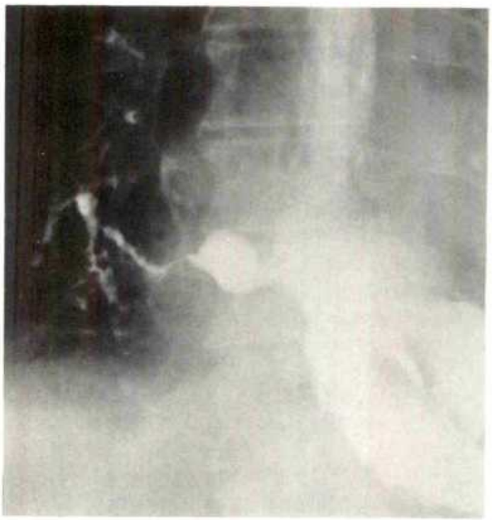

Figure 1 *An oesophagogram shows communication between the oesophagojejunal junction and the bronchial tree*

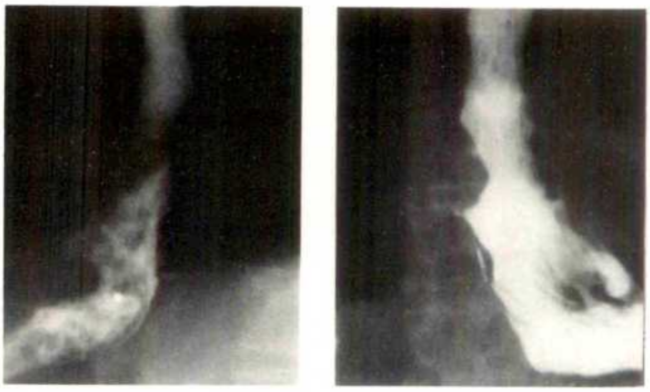

Figure 2 *Fistula closed after injection of glue*

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Paper accepted 17 November 1986

0007–1323/87/050415–01$3.00

Br. J. Surg. 1987, Vol. 74, May, 416–419

Clinical implications of abnormal oesophageal motility

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The usefulness of oesophageal manometry as a clinical tool has been assessed in 202 patients requiring detailed investigation for troublesome oesophageal symptoms, who first presented between June 1979 and May 1982. Only 12 were found to have specific motility disorders such as achalasia and scleroderma. A total of 147 had a variety of non-specific motility disorders and, of these, 112 (76·2 per cent) had coexistent gastro-oesophageal reflux. There was a significant association between the symptoms of dysphagia and the occurrence of predominantly non-propagated motor activity in the oesophagus. A similarly significant relationship existed between crushing chest pain and oesophageal spasm. Despite this statistical association, detection and treatment of gastro-oesophageal reflux was found to be the most useful part of clinical management. Symptoms of associated motility disorders resolved in more than 90 per cent of patients treated by Nissen fundoplication. Pre-operative assessment of motility was of no value in detecting those who might develop postoperative dysphagia. Oesophageal manometry is useful for the assessment of a small proportion of patients with oesophageal symptoms in whom gastro-oesophageal reflux has been excluded by vigorous investigation, including 24 h pH recording.

Keywords: Oesophageal motility, gastro-oesophageal reflux, Nissen fundoplication

Oesophageal motility disorders have been suggested as a cause of chest pain which may be confused with angina pectoris[1,2]. In addition, the description of new motility disorders such as the 'nutcracker oesophagus'[3], which is characterized by peristaltic contractions of high pressure and long duration, has increased the numbers of patients whose chest pain is attributed to an oesophageal cause. It has also been suggested that all patients who are about to undergo surgery for control of gastro-oesophageal reflux should have a pre-operative motility study to detect those at risk of developing postoperative dysphagia[4–6]. Despite this, the usefulness of oesophageal manometry in clinical practice has been challenged[7] and most surgical gastroenterologists do not use it for either diagnosis or pre-operative screening.

In an attempt to clarify matters in our own practice we have studied a cohort of 202 patients who first presented between June 1979 and May 1982. All presented with severe symptoms suggestive of oesophageal disease sufficient to justify extensive investigation. They were studied by oesophageal manometry and prolonged recording of lower oesophageal pH, as well as by conventional investigations of the upper gastrointestinal tract. Our aim was to assess the incidence and significance of particular patterns of abnormal motility in a mixed group of patients typical of those seen by most gastroenterologists. We were also interested in the effect of surgical treatment for gastro-oesophageal reflux on coexistent motility disorders and the possible deleterious effects of surgery in patients with severe motility disorders.

Patients and methods

A total of 202 consecutive adult patients presenting with symptoms of chest pain, abdominal pain or dysphagia were studied. The diagnostic protocol was as follows:

1. A detailed history was taken and physical examination performed. Particular attention was paid to the symptoms of crushing central chest pain and dysphagia which might be caused by abnormal motility. An endoscopy to detect cancer, stricture or oesophagitis was performed as soon as possible. Patients with cancer were excluded from further study. A barium swallow and meal was carried out in selected cases (146) to provide further information about oesophagogastric anatomy and function.
2. Oesophageal motility was studied by oesophageal manometry.
3. Intra-oesophageal pH was monitored to detect gastro-oesophageal reflux.

Dysphagia was defined as the sensation of food sticking in the oesophagus, this being terminated by either regurgitation or delayed passage into the stomach. The sensation of a persistent lump in the oesophagus, sometimes called pseudodysphagia, was ignored as this symptom is poorly understood.

Oesophageal manometry

High fidelity manometric tracings were made with conventional low compliance equipment. A commercially available multilumen manometry catheter was used (Arndorfer Medical Specialties, Greendale, Wisconsin, USA) with three radially spaced side holes 5 cm from the tip and two further openings at 5 cm intervals. The catheter channels were perfused continuously with water delivered by an Arndorfer pneumohydraulic pump, connected to Statham P23 pressure transducers and recordings made on a Grass polygraph. The manometry catheter was withdrawn at 1 cm intervals to measure the lower oesophageal sphincter pressure and to assess motility in the body of the oesophagus. At each stage several wet (10 ml water) and dry swallows were observed. The examination was carried out in a leisurely fashion taking 1–2 h to allow adequate time for the patient to settle and for a proper assessment of abnormal activity which might be associated with symptoms. All non-essential medication was stopped 24 h before the test.

The conduct of the examination and the interpretation of the manometry traces were based on the account by Hurwitz, Duranceau and Haddad[8] and also that by Henderson[9]. Non-specific motility disorders were classified descriptively as follows:

1. Predominantly non-propagated activity; more than 50 per cent of swallows failed to initiate a propagated peristaltic wave, but no other features of diffuse oesophageal spasm.
2. Damped peristalsis: diminution of the amplitude of peristalsis by at least 25 per cent as it passed distally in the oesophagus.
3. Spontaneous activity: spontaneously occurring non-propagated

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(tertiary) contractions at an average frequency of more than 1 per minute.

4. Spasm was diagnosed if one or more of the following criteria were met:
   (a) frequent, non-propagated, spontaneous contractions associated with baseline pressure rise[1]
   (b) amplitude of peristalsis greater than 125 mmHg[1,3]
   (c) duration of peristalsis greater than 7·5 s [1]
   (d) repetitive contractions after deglutition[10].

Normal values in our own laboratory, based on a study of 30 asymptomatic subjects, are: >90 per cent of swallows initiate propagated peristalsis; peristaltic wave amplitude 57·2±8·3 mmHg (mean±s.d.); duration of contraction 6±1·9 s; 1·76±1·2 tertiary contractions during 5 min of quiet respiration. These values are similar to those reported by Duranceau *et al.*[11].

Oesophageal pH measurement

Most studies were carried out using a Radiometer gastric pH electrode (type GK 282/c) which incorporates a reference electrode. The tip of the probe was positioned 5 cm above the upper level of the manometrically determined lower oesophageal sphincter. Reflux provocation tests were then performed as described by Ismail-Beigi and Pope[12] before and after loading the stomach with 200–250 ml 0·1 M hydrochloric acid. After the provocation test, oesophageal pH was monitored for a prolonged period, usually 3·00 p.m. to 9·00 a.m. the following morning. Traces were analysed as suggested by Johnson and DeMeester[13] to identify those with pathological reflux.

Statistical methods

The results were assessed by χ^2 analysis with Yates' correction for continuity. Fisher's exact probability test was used when a cell in a contingency table contained a value of 5 or less.

Results

The patient population was typical of those causing diagnostic difficulty; 47 had completely normal appearances both at endoscopy and barium screening. In most of the remainder the findings on conventional investigation were of questionable significance, e.g. small hiatus hernia but no reflux, or slight reddening of the lower oesophagus.

Only 12 of the 202 patients investigated had specific motility disorders. There were four cases of achalasia, four of idiopathic (symptomatic) diffuse oesophageal spasm and two cases of scleroderma. One patient had a steroid-induced myopathy causing marked oropharyngeal dysphagia and another had a disorder similar to diffuse spasm which was related to chronic ingestion of chlormethiazole and which resolved when the drug was stopped. The four cases of achalasia had classical X-ray and endoscopic findings, but manometry was essential for diagnosis in the remainder of the above cases. A total of 147 patients had non-specific motility disturbances as shown in *Table 1*. Gastro-oesophageal reflux was a common finding in every group. There was a particularly high prevalence in those with damped peristalsis which is not surprising as this abnormality is known to be an effect of reflux[14].

There was a significant association between symptoms and two of the manometric groups. Patients with predominantly non-propagated motor activity were more likely to experience dysphagia (*Table 2*) and those with spasm were more likely to experience central chest pain (*Table 3*) than the group as a whole. There was not, however, a one-to-one correlation between symptoms and manometric abnormality.

No further subdivision of the group with spasm was useful in understanding symptoms nor did any motility pattern seem to imply a particular clinical course. Of particular interest is the fact that five of seven patients with the 'nutcracker' abnormality had gastro-oesophageal reflux.

Effect of reflux control by surgery

Because of our scepticism about the value of smooth muscle relaxants and of surgical myotomy in patients with motility disorders other than achalasia, most of our therapeutic efforts were directed towards controlling gastro-oesophageal reflux whenever it was present. This policy was followed whether the patient's symptoms were typical of reflux or not. When vigorous medical management with H_2-receptor antagonists, antacid/alginate preparations and cholinergic drugs failed to control persistently severe symptoms, an antireflux operation was recommended. The sudden cessation of reflux by an operation provides a convenient model to assess the effects of reflux on symptoms and motility. Sixty-one patients had a Nissen fundoplication, 55 being performed by the senior author (J.B.) and 6 by other consultant surgeons in Hope Hospital. In every case, particular attention was paid to producing a loose and short fundoplication to minimize postoperative side-effects[15]. Follow-up of the cases ranged from 3–6 years. Postoperative endoscopy was undertaken in every case and manometry and pH studies were performed approximately 6 months after operation in 36 patients who agreed to the tests. Those who did not agree to have manometry and pH studies had a barium meal. Persistent reflux was demonstrated in four patients (pH monitoring two, barium meal two) and three of the four had persistent symptoms. No patient had persistent oesophagitis.

The symptoms for which oesophageal motility studies are most likely to be recommended are dysphagia in the absence of a stricture, and chest pain of a crushing or constricting character.

Table 2 *Relationship between non-propagated contractions and dysphagia*

	Dysphagia	No dysphagia
Propagated peristalsis	32	129
Non-propagated activity	6	5

The 172 cases listed exclude those with specific motility disorders and those with possible organic obstruction of the oesophagus
$P = 0·0157$, Fisher's exact test

Table 3 *Relationship between spasm and chest pain (same patients as in* Table 2)

	Chest pain	No chest pain
No spasm	34	98
Spasm	20	20

χ^2 (Yates' correction) = 7·288, $P < 0·01$

Table 1 *Non-specific motility disturbances*

Motility disorders	Total no.	With dysphagia (%)	With chest pain (%)	With reflux (%)
Predominantly non-propagated activity	11	6 (54·5)	3 (27·3)	8 (72·7)
Damped peristalsis	25	5 (20·0)	6 (24·0)	24 (96)
Spontaneous activity	45	4 (8·9)	10 (22·2)	27 (60)
Damped peristalsis and spontaneous activity	26	5 (19·2)	9 (34·6)	23 (88·5)
Spasm	40	12 (30)	20 (50)	30 (75)
Total	147	32 (21·8)	48 (32·7)	112 (76·2)

Twenty-four patients had dysphagia before operation and 24 had chest pain. One year after operation dysphagia had resolved in all but two cases ($P<0{\cdot}001$, highly significant) and only one had persistent chest pain ($P<0{\cdot}001$). Chest pain usually resolved quickly after operation, but dysphagia sometimes persisted for several months (*Table 4a*). Despite the resolution of symptoms significant manometric change was rarely seen. Only three of the 36 patients tested postoperatively demonstrated a return to normal motility.

Apart from those with achalasia or idiopathic diffuse oesophageal spasm, no patient with a motility disorder not associated with gastro-oesophageal reflux had persistently severe chest pain or dysphagia. Treating reflux therefore dealt with the majority of those with severe symptoms.

Twenty-eight patients had never experienced dysphagia before operation and 19 (67·9 per cent) developed the symptom afterwards. This usually resolved quite quickly, but even after one year, three patients (10·7 per cent) still had persistent dysphagia (*Table 4b*). In two of these cases the dysphagia was severe and on exploration both were found to have constriction of the oesophagus by scar tissue at the hiatus. In the remaining patients dysphagia was intermittent and not particularly troublesome. None of those who developed dysphagia after operation had a severe motility disorder before operation.

Discussion

We believe that the current emphasis on detecting oesophageal motility disorders is somewhat misdirected as detailed studies seldom lead to improved clinical management. There is little doubt that abnormal motility may produce symptoms, but most of the time the abnormality is associated with gastro-oesophageal reflux and treatment of the reflux will improve the symptoms. Others have suggested that oesophageal manometry is clinically useful[10,16], but failed to show how this results in improved patient management and have not performed prolonged pH recording. It has also been suggested that manometry should always precede surgery for gastro-oesophageal reflux to avoid the risk of precipitating obstructive symptoms in those with poor motility[4–6]. This risk is probably largely confined to those with scleroderma, achalasia and those with 'end-stage' reflux disease who may have an aperistaltic oesophagus. In practice, most of these patients will be detected by clinical suspicion and by an adequate barium study. In any case such patients are rare.

The results of our own study suggest that assessment of gastro-oesophageal reflux is the most useful line of investigation for any patient with severe oesophageal symptoms which cannot be explained after careful endoscopy and barium studies. By ignoring abnormalities of motility and concentrating on the diagnosis and control of reflux, chest pain and dysphagia were managed in more than 90 per cent of our patients. In addition, there was no suggestion that severe motility disorders might be associated with postoperative oesophageal obstruction. This is not to say that postoperative dysphagia did not occur, simply that manometry did not give any warning of the problem. It is important to emphasize, however, that we would still recommend care in patients with a completely aperistaltic oesophagus. Some of these, especially those with scleroderma, are probably best managed by special techniques such as fundoplication gastroplasty[17], but a properly constructed floppy Nissen shold not produce obstruction.

It is now well established that gastro-oesophageal reflux may provoke oesophageal motility disturbances. Acid infusion into the oesophagus, as in a Bernstein test, may result in altered motility[18,19]. In 1965, Olsen and Schlegel described three types of abnormal motility—motor incoordination, weak contractions and motor failure—which they found in patients, with oesophagitis[20]. Hypermotility disorders, as in our group with spasm, have not been so well described. There is also uncertainty about the reversibility of motility disorders associated with relux. Russell *et al*[21] could not document any improvement in oesophageal transit following antireflux surgery and, in our own patients, only 3 of 36 had their motility restored to normal. It is, of course, possible that fundoplication, may itself alter motility and perhaps the disturbance of the operation may take a long time to disappear, hence the incidence of postoperative dysphagia in the present series.

Primary disorders of oesophageal motility are uncommon and, apart from achalasia, scleroderma and diffuse oesophageal spasm, are rarely associated with severe symptoms. We would suggest that those who claim to describe 'new' motility disorders must rigorously exclude gastro-oesophageal reflux as a cause of oesophageal symptoms by 24 hour pH recording. Even a disorder as dramatic as diffuse oesophageal spasm may be a non-specific response to a variety of insults[22]. It would also seem prudent to demonstrate that the disorder is confined to the oesophagus and not associated with the irritable bowel syndrome[23].

Oesophageal manometry is a specialized investigation which is useful for the occasional patient with an undiagnosed primary motility disorder. We would agree with Meshkinpour *et al.*[7] that the widespread use of manometry as a clinical tool is not cost effective, although it does have a place in specialized units. The surgical gastroenterologist is better advised to invest his money in equipment for pH recording.

Table 4 **a** *Effect of Nissen fundoplication on 24 patients with dysphagia which was not due to organic obstruction of the oesophagus*

a	Dysphagia (%)	No dysphagia (%)
Immediately postoperation	13	11 (45·8)
6 months	7	17 (70·8)
12 months	2	22 (91·7)

b *Incidence of postoperative dysphagia in 28 patients with no dysphagia before operation*

Immediately postoperation	19 (67·9)	9
6 months	6 (21·4)	22
12 months	3 (10·7)	25

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Paper accepted 30 November 1986

Surgical workshops

Br. J. Surg. 1987, Vol. 74, May, 419

Air insufflation test: a new method of assessing correct placement of a permanent endo-oesophageal tube

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Peroral pulsion intubation of malignant strictures of the oesophagus using a permanent endo-oesophageal tube is an established technique[1,2]. Pulsion intubation has been shown to be superior to the traction method[1,3] but still suffers from a major drawback in its potential for oesophageal perforation in what is essentially a 'blind' procedure. We have one of the highest incidences of oesophageal carcinoma in the world, a resection rate of only 6 per cent, and as many as 10 to 15 intubations at two endoscopy sessions per week, so we recognized the need for a reliable intra-operative test to check correct tube placement.

Technique

A 20 French gum-elastic bougie is passed through the malignant stricture and serves as a pilot over which the permanent endo-oesophageal tube is passed. The tube is then pushed, using the oesophagoscope as a ram, to the level of the stricture as determined at preliminary oesophagoscopy. The pilot bougie is removed without withdrawing the oesophagoscope from its position of contact with the tube. A tight-fitting tube is connected to the oesophagoscope (usually a small cuffed endotracheal tube) and gas is blown into the oesophagus while the surgeon auscultates over the epigastrium with a stethoscope (*Figure 1*). Air insufflation of the stomach has a distinctive note and indicates correct tube placement. The air insufflation test is an easy, safe and reliable method of determining correct tube placement, and the answer is obtained immediately.

The reported incidence of oesophageal perforation during pulsion intubation is 2·5 to 7·1 per cent. Our incidence in the last 120 cases is 6 per cent. Apart from the definite risk of exiting the gastrointestinal tract, the tube may be placed too high or too low in relation to the structure or may be kinked. Early detection of incorrect placement allows the surgeon to remove and reposition the tube forthwith without recourse to any other investigations and the need for a further general anaesthetic. A delay of even 4 to 6 h from the time of oesophageal injury to subsequent corrective action usually sets the stage for serious complications with often a fatal outcome.

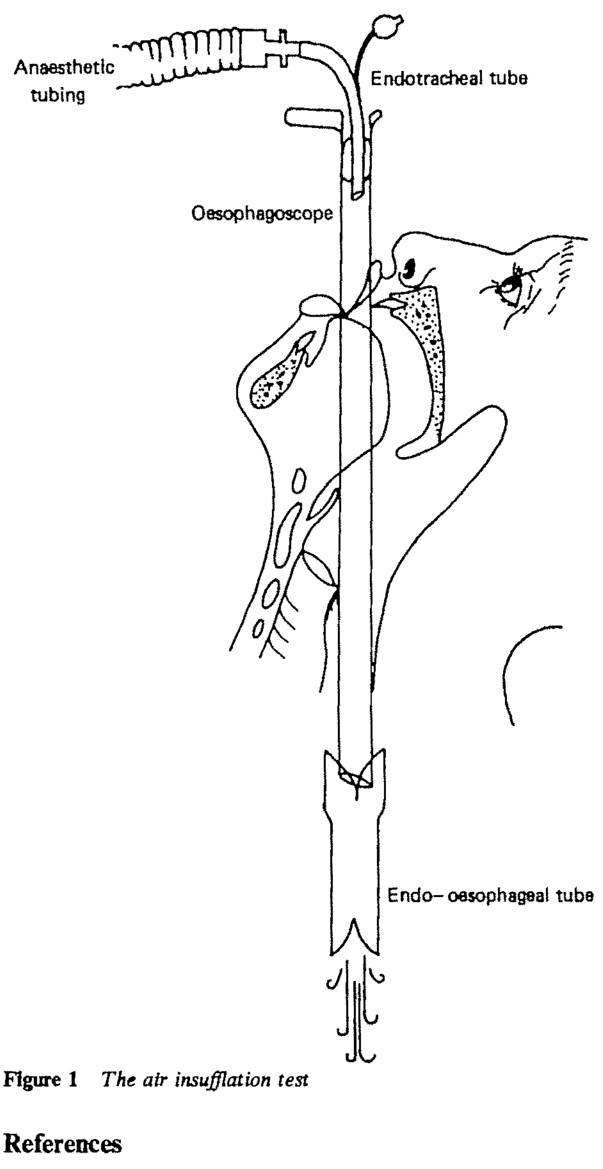

Figure 1 *The air insufflation test*

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Paper accepted 1 December 1986

0007–1323/87/050419–01$3.00

Br. J. Surg. 1987, Vol. 74, May, 420

Treatment of hidradenitis suppurativa with the carbon dioxide laser

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Hidradenitis suppurativa is a chronic inflammatory disease of the apocrine sweat glands. Patients suffer recurrent infections of these glands in the axillae, groin and perineal areas. Response to conservative therapy is unpredictable and often short-lived though recent reports of improved success with isotretinoin[1] offer some encouragement. Surgical excision, often of extensive areas of skin, with skin grafting, healing by granulation or flap formation is still the mainstay of treatment in most centres[2-4]. We have treated six patients with this disease with the carbon dioxide laser from 1980 to 1985. Two further patients are currently undergoing treatment. The method of treatment and results are presented.

Patients and methods

Patients

The patients' ages ranged from 20 to 43 years and all were female except for the youngest. They had had recurrent disease for up to 12 years at more than one site, including axillae, groin, perineum and thighs. One patient had never been treated and two had had antibiotics only. The remainder had also had multiple surgical procedures including abscess drainage, grafting (failed) and radiotherapy.

Method

Laser technique. The laser used was a Coherent System 400 carbon dioxide laser usually used in the department to treat pre-invasive carcinoma of the cervix. The laser was focused on the area to be treated and the tissue vaporized to a depth of between 3 and 8 mm. The depth varied with the amount of scar tissue present and the size of any pus collections. The tissue was vaporized until no further pus flowed from the lesions and all thickening and scarring had been obliterated. This occasionally resulted in exposure of subcutaneous fat. Because the laser is a narrow beam (1·6 mm), there is no damage to surrounding tissue. Saucerization of the area (*Figure 1*) allowed better healing. The treatment is rapid, taking about 1 min to treat each abscess or scarred area. Multiple small areas can be vaporized at a session. Blood loss is negligible, the laser being haemostatic.

Number of treatments. Where there were wide areas involved, it was decided to treat patients at more than one session rather than remove large areas of skin at one time. Two patients required a single session only, the rest needing from two to four sessions to eradicate all of their affected areas. Three of these returned with new disease in other areas from 1 to 4 years later which was similarly treated, one patient finally having 7 sessions.

Postoperative care. At operation, the laser 'craters' were dressed with Melolin gauze. Patients were given adequate analgesia and discharged home with Melolin dressings and instructions to keep the wounds clean and dry. Prophylactic antibiotics were not prescribed.

Postoperative course. The wounds all healed by granulation in between 3 and 7 weeks, depending on the size of the skin defect. No patient had a wound infection and all patients felt that the postoperative pain was less than the disease and less than that of previous surgical procedures. One patient who had had a large area of skin removed at the first treatment experienced considerable pain after this treatment only.

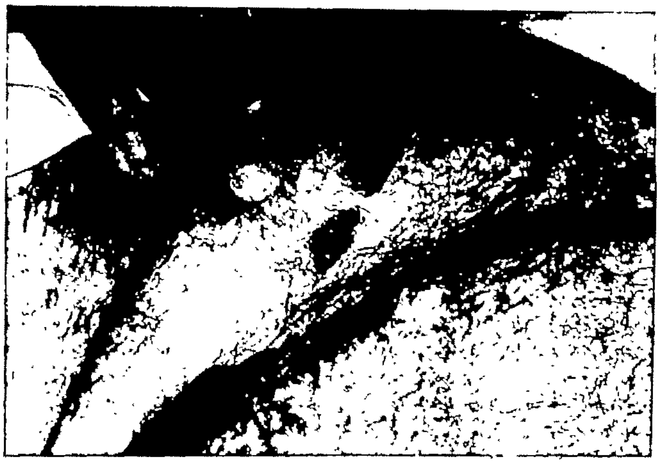

Figure 1 *Lasering to suprapubic area showing the 'saucerized' laser crater to a depth of 5 mm and the smoke extractor*

Follow-up. All patients are currently disease-free having been reviewed for between 9 months and 3 years. All were asked their opinions about the scarring after treatment and they were unanimous that it was far less than both the disease and that after surgery. The recurrences have all been in areas not previously treated.

Discussion

Hidradenitis suppurativa remains a disease which causes much morbidity. The technique of treatment outlined above has several advantages over previous regimens. It requires the patients to be admitted only as day patients, at most overnight, in marked contrast to the length of time necessary with the other surgical procedures employed in this disease. The healing time was not prolonged and no patient had any wound infection. The pain from the treatment was within acceptable limits and never worse than that of the disease itself. The scarring from laser treatment was a significant improvement over that occurring following conservative and surgical methods. It is felt that this treatment is an advance in the management of this disease.

Acknowledgements

Dr J. C. Dalrymple was supported and the laser provided by the Evening Chronicle Laser Research Fund.

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Paper accepted 10 September 1986

0007–1323/87/050420–01$3.00

Br. J. Surg. 1987, Vol. 74, May,
421–426

Effects of epidural administration of local anaesthetics or morphine on postoperative nitrogen loss and catabolic hormones

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To examine the effects of postoperative epidural analgesia with local anaesthetics or morphine on the excess nitrogen loss after upper abdominal surgery and to assess the roles of catabolic hormones in the nitrogen loss, urinary excretion of nitrogen and catecholamines and plasma concentrations of cortisol and glucagon were measured in three groups of patients undergoing elective gastrectomy. Group G patients received the operation under general anaesthesia, and their postoperative pain was relieved by intermittent injections of analgesics. Group PE received prolonged epidural analgesia with local anaesthetics during and after surgery. Group EM received epidural analgesia intra-operatively and epidural morphine postoperatively. Urinary nitrogen excretion during the first three postoperative days was significantly less in the PE and EM groups than in the G group, and the PE group excreted slightly less nitrogen than the EM group. In the G group, urinary excretion of adrenaline increased mainly on the day of operation, and noradrenaline chiefly on postoperative days. These catecholamine responses were almost completely abolished in the PE group, and significantly inhibited in the EM group. Plasma cortisol response was most remarkable shortly after the operation and then decreased in all groups, but was significantly lower in the two epidural groups than in the G group throughout the study. Plasma glucagon increased postoperatively in all groups, and the increase was less pronounced in both epidural groups than in the G group. These results suggested that an elevated sympathetic activity, represented by increased noradrenaline excretion and elicited by painful nociceptive and sympathetic nervous afferents, is responsible for the postoperative nitrogen loss which is mediated by glucagon and cortisol.

Keywords: Epidural, morphine, nitrogen metabolism, catecholamines

Negative nitrogen balance is a central feature of the metabolic response to major surgery, but the mechanism has not been well understood. Brandt *et al.*[1] have reported that postoperative nitrogen balance was better in patients having lower abdominal surgery under epidural analgesia than in those having general anaesthesia. Their results suggest that neural stimuli arising from the operative site initiate the negative nitrogen balance by producing various endocrine responses.

In upper abdominal surgery, however, Seeling *et al.*[2] and Hjortsø *et al.*[3] could not demonstrate the protein-sparing effect of epidural analgesia and postulated that the greater stress of upper abdominal or thoraco-abdominal surgery was less well relieved by epidural analgesia.

In the present study, we examined the effect of epidural administration of local anaesthetics or morphine on the postoperative nitrogen loss in patients undergoing elective gastrectomy, in an attempt to differentiate the role of painful nociceptive and of sympathetic nervous stimuli in the nitrogen loss. We also attempted to elucidate the relationships between the postoperative nitrogen loss and the endocrine responses which are known to be modified by epidural analgesia[4–7].

Patients and methods

Seventy patients undergoing elective gastrectomy for cancer or ulcer were studied. None of them had any metabolic or endocrine disturbances, hepatic or renal diseases, neither had they received any medication pre-operatively. Urinalysis was normal in all patients. Informed consent to participate in the study was obtained from all patients.

The patients were randomly allotted to either a general anaesthesia group (G group, $n = 30$) or an epidural analgesia group which was subdivided into a prolonged epidural group (PE group, $n = 20$) and an epidural morphine group (EM group, $n = 20$) according to the methods used for postoperative pain-relief. Characteristics of the three groups of patients are shown in *Table 1*. The G group patients were slightly younger than the other two groups but there was no significant difference in any respect.

Table 1 *Characteristics of the patients*

	G group	PE group	EM group
n	30	20	20
Sex: male/female	20/10	13/7	15/5
Disease: cancer/ulcer	25/5	15/5	19/1
Gastrectomy: partial/total	22/8	16/4	12/8
Age (years)	57±2	62±2	63±3
Body height (cm)	159±1·7	157±1·8	157±1·3
Body weight (kg)	54±2·0	53±2·0	50±1·5
Operation time (min)	193±9	189±11	208±13
Blood loss (ml)	544±68	477±76	433±58)

Figures are number of patients, mean values are group mean ±s.e.m.; G group, general anaesthesia group; PE group, prolonged epidural group; EM group, epidural morphine group

0007-1323/87/050421-05$3.00 © 1987 Butterworth & Co (Publishers) Ltd

Medication and anaesthesia

Premedication with droperidol 2·5 mg, pethidine 1 mg/kg body weight and atropine 0·5 mg was given in each patient 1 h before surgery which was started in the morning after an overnight fast. The G group patients received the operation under general anaesthesia with halothane–nitrous oxide–oxygen mixture given under endotracheal intubation and their postoperative pain was relieved by intermittent injections of analgesics according to patients' requests. Both epidural groups' patients were operated on using continuous epidural analgesia with 0·5 per cent bupivacaine, extending from T_{3-4} to L_{1-2}, and were sedated by intravenous diazepam injections during the operation. No general anaesthesia was used in these groups of patients.

Postoperatively, the PE group patients received continuous injections of 3–5 ml/h 0·5 per cent bupivacaine through an epidural catheter using an infusion pump until the third postoperative day. Hypotension associated with epidural blockade was treated by intravenous injections of etilefrine hydrochloride (Effortil) when indicated. In the EM group, 4 mg morphine in 10 ml saline was injected through the epidural catheter, starting 1 h after surgery and then every 12 h for 3 postoperative days. The PE and EM group patients were completely pain free postoperatively, requiring no additional systemic analgesics. Detailed techniques of general anaesthesia and epidural analgesia were described previously[6].

In all groups, intra-operative infusion was restricted to lactated Ringer solution and citrated whole blood when blood loss was excessive. Postoperative infusion therapy consisted of electrolyte solution, glucose solution and fat emulsion, equivalent to 15 kcal kg^{-1} day^{-1}, given for 3 days. Fat emulsion was used intending to provide more calories without increasing excess fluid, in a daily amount of 200 ml 10 per cent solution.

Samples and laboratory tests

In each patient, urine samples were collected every 24 h to measure nitrogen and catecholamines, starting on the day before operation and continuing until the third postoperative day. Peripheral venous blood samples were withdrawn for measurement of plasma cortisol and glucagon before pre-anaesthetic medication, at about 1 h after skin incision (time A), at about 2 h after skin incision (time B), at about 30 min after completion of surgery (time C) and at 8 a.m. on the first three postoperative days.

Urinary nitrogen was measured by micro-Kjeldahl method, and catecholamines were determined using high-speed ion-exchange column chromatography and the automated trihydroxyindol method as described by Victora *et al*[8]. with slight modification. Plasma cortisol was measured by radioimmunoassay using the 'Gamma Cort' cortisol kit (Clinical Assay Co.), and glucagon by radioimmunoassay using the pancreatic glucagon-specific antibody[9].

Statistical analysis

All data are expressed as the mean ± s.e.m. Statistical analysis was performed using the paired and unpaired Student's *t* test or Wilcoxon ranks sum test. *P* values < 0·05 were considered statistically significant.

Results

Urinary nitrogen

Urinary nitrogen excreted on the pre-operative day and during the first 3 postoperative days is shown in *Table 2*. The pre-operative values of nitrogen excretion are considerably less than those reported, which may be due to a lesser muscle mass and a lower protein intake in our patients. Urinary nitrogen increased after gastrectomy in all groups, but both epidural groups excreted less nitrogen than the G group. The differences were significant between the G group and the other two epidural groups on the second postoperative day, and between the G and PE groups on the third postoperative day. Cumulative nitrogen excretion for 3 days postoperatively was significantly less in the two epidural groups than in the G group. Comparing the two epidural groups, there was no statistically significant difference in nitrogen excretion.

Endocrine response

Urinary excretion of adrenaline was remarkably increased in the G group on the day of surgery and then decreased rapidly (*Table 3*). This urinary adrenaline response was completely inhibited in the PE group, and that in the EM group was between the other two groups. On the day of operation and on the first postoperative day, differences were significant among these three groups.

Urinary noradrenaline increased chiefly on postoperative days in all groups (*Table 4*). This noradrenaline response was the largest in the G group and the least in the PE group, and that in the EM group was between. Differences between the G and the two epidural groups were significant throughout the study, and that between the PE and the EM group was significant only on the first postoperative day.

Plasma cortisol concentrations were consistently and significantly lower in the two epidural groups than in the G group throughout the study period (*Table 5*). Cortisol concentrations gradually decreased in the postoperative period, and those in the EM group were slightly lower than in the PE group.

Plasma glucagon data are shown in *Table 6*. For an unknown reason, glucagon concentrations in the PE group were consistently lower than those in the other two groups. It was found, however, that glucagon tended to increase in the postoperative period in all groups and that the postoperative increase was attenuated by postoperative epidural administration of local anaesthetics or morphine. When the percentage increase in peak values above control levels was compared, it was 80 per cent in the G group, 55 per cent in the EM group and 50 per cent in the PE group.

Table 2 *Urinary nitrogen excretion (mg kg^{-1} body weight day^{-1})*

Group	Pre-operative day	Postoperative days 1	2	3	Cumulative nitrogen loss (1–3 days)
G group					
n	12	30	30	30	30
Mean	84 ± 9·8	177 ± 10·4	193 ± 14	175 ± 12	545 ± 27
PE group					
n	10	20	20	20	20
Mean	100 ± 17	144 ± 14	136 ± 11	132 ± 12	414 ± 30
P (*versus* G)	n.s	n.s	<0·01	<0·05	<0·01
EM group					
n	18	20	20	20	20
Mean	98 ± 10·7	149 ± 11	145 ± 8	142 ± 11	436 ± 24
P (*versus* G)	n.s.	n.s.	<0·01	n.s.	<0·01
P (*versus* PE)	n.s.	n.s.	n.s.	n.s.	n.s.

Values are mean ± s.e.m.
G group, general anaesthesia group; PE group, prolonged epidural group; EM group, epidural morphine group

Table 3 *Urinary adrenaline excretion (μg/day)*

Group	Pre-operative day	Day of operation	Postoperative days		
			1	2	3
G group					
n	29	30	29	29	11
Mean	7·1±1·5	39·4±3·8	18·7±2·0	11·2±1·4	11·5±2·7
PE group					
n	18	20	20	20	15
Mean	6·3±0·9	7·8±1·4	8·8±1·5	7·1±1·0	6·9±1·1
P (*versus* G)	n.s.	<0·01	<0·01	<0·05	n.s.
EM group					
n	20	20	20	20	20
Mean	6·3±0·9	18·0±3·5	14·7±2·1	10·6±1·9	9·8±2·2
P (*versus* G)	n.s.	<0·01	n.s.	n.s.	n.s.
P (*versus* PE)	n.s.	<0·05	<0·05	n.s.	n.s.

Values are mean±s.e.m.
G group, general anaesthesia group; PE group, prolonged epidural group; EM group, epidural morphine group

Table 4 *Urinary noradrenaline excretion (μg/day)*

Group	Pre-operative day	Day of operation	Postoperative days		
			1	2	3
G group					
n	29	30	29	29	11
Mean	43·9±5·2	90·1±7·5	126·2±10·9	119·9±12·4	106·7±14·8
PE group					
n	18	20	20	20	15
Mean	43±5·6	44·8±4·2	55·6±5·8	60±7·6	51·6±5·6
P (*versus* G)	n.s.	<0·01	<0·01	<0·01	<0·01
EM group					
n	20	20	20	20	20
Mean	48±8·9	55·4±6·2	86±7·1	80±6·7	71±7·3
P (*versus* G)	n.s.	<0·01	<0·01	<0·01	<0·05
P (*versus* PE)	n.s.	n.s.	<0·01	n.s.	n.s.

Values are mean±s.e.m.
G group, general anaesthesia group; PE group, prolonged epidural group; EM group, epidural morphine group

Postoperative course

All patients tolerated the operation well and recovered without any major postoperative complications.

Discussion

Our present results demonstrate that postoperative nitrogen loss in patients receiving elective gastrectomy was significantly reduced by prolonged epidural blockade with local anaesthetics. These results contrasted with those reported previously[2,3] in which epidural blockade failed to improve nitrogen balance in patients undergoing major abdominal or thoraco-abdominal surgery. Reasons for the discrepancy between our results and those reported by others are not clear but may be due to the inclusion of different operations[2] or insufficient sympatho-adrenal blockade[3] in these reports. In our study, the homogeneity of the patients studied and effective epidural blockade, as indicated by the absence of catecholamine response, may have accounted for the significant reduction of nitrogen loss in the PE group.

Our results show that effective pain relief with postoperative epidural morphine also reduces nitrogen loss, although to a slightly lesser degree as compared with epidural local anaesthetics, suggesting that painful nociceptive nervous stimuli produce protein catabolism. This result is in accordance with Masek and Horky[10] who showed a significant decrease in nitrogen retention during the period of pain in patients with nervous diseases in whom there was little gross tissue injury. In our results nitrogen excretion in the EM group was slightly greater than in the PE group, which may be due to sympathetic afferent left unblocked by epidural morphine.

Our attempt to elucidate the roles of catabolic hormones showed that urinary adrenaline excretion increased in the G group mostly on the day of surgery, indicating that the adrenal medulla is stimulated mainly during and shortly after the operation. This adrenaline response was completely abolished in the PE group, and significantly inhibited in the EM group. The moderate increase of adrenaline excretion in the EM group may be due to sympathetic activity that recovered after the epidural blockade finished. On postoperative days when nitrogen excretion was increased, urinary adrenaline decreased in all groups and returned to control levels by the second postoperative day, even in the G group. These results suggest that adrenaline may not be responsible for the postoperative nitrogen loss.

In contrast, noradrenaline excretion increased mainly on postoperative days, being coincidental with the increase in nitrogen excretion. Furthermore, the inhibition of noradrenaline excretion with epidural administration of local anaesthetics or morphine was grossly correlated with that of nitrogen excretion. Since noradrenaline excretion represents sympathetic nervous activity, these results may indicate that an increased sympathetic activity may be an important factor in the postoperative nitrogen loss. Painful nociceptive stimulus is a strong activator of the sympathetic nervous function, which may explain why nitrogen and noradrenaline excretion were inhibited with epidural morphine in our results.

Changes in plasma glucagon also corresponded with nitrogen loss in that glucagon concentrations increased on

Table 5 *Plasma cortisol concentrations (nmol/l)*

Group	Before pre-medication	Time of sampling A	B	C	Postoperative days 1	2	3
G group							
n	30	30	30	30	29	28	25
Mean	385±30	760±32	857±41	925±41	818±68	592±34	559±30
PE group							
n	20	20	19	20	20	19	20
Mean	344±22	578±29	666±29	658±41	512±30	454±38	462±36
P (*versus* G)	n.s.	<0·01	<0·01	<0·01	<0·01	<0·05	<0·05
EM group							
n	20	20	20	20	20	20	20
Mean	311±23	554±22	642±26	699±37	396±33	402±32	399±35
P (*versus* G)	n.s.	<0·01	<0·01	<0·01	<0·01	<0·01	<0·01
P (*versus* PE)	n.s.	n.s.	n.s.	n.s.	<0·05	n.s.	n.s.

Values are mean±s.e.m.
G group, general anaesthesia group; PE group, prolonged epidural group; EM group, epidural morphine group; time A, about 1 h after skin incision; time B, about 2 h after skin incision; time C, 30 min after completion of the procedure

Table 6 *Plasma glucagon concentrations (pg/ml)*

Group	Before pre-medication	Time of sampling A	B	C	Postoperative days 1	2	3
G group							
n	24	24	24	24	23	22	21
Mean	99±7·5	111±8·1	96±6·9	110±8·7	160±16·8	180±14·7	141±11·5
PE group							
n	18	18	18	18	18	18	18
Mean	69±5·6	68±5·6	62±5·8	63±5·8	103±8·0	90±8·0	89±6·8
P (*versus* G)	<0·01	<0·01	<0·01	<0·01	<0·01	<0·01	<0·01
EM group							
n	19	19	19	19	19	19	19
Mean	90±14·9	96±12·6	94±12·3	86±14·5	140±17·6	136±16·7	108±14·2
P (*versus* G)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
P (*versus* PE)	n.s.	n.s.	<0·05	n.s.	n.s.	<0·05	n.s.

Values are mean±s.e.m.
G group, general anaesthesia group; PE group, prolonged epidural group; EM group, epidural morphine group; time A, about 1 h after skin incision; time B, about 2 h after skin incision; time C, 30 min after completion of the procedure

postoperative days and were inhibited by epidural local anaesthetics or epidural morphine. Glucagon produces hepatic gluconeogenesis and ureagenesis[11], and is reportedly released by stimulating the sympathetic zone of the hypothalamus[12]. Glucagon may be thus considered playing an important role in the postoperative nitrogen loss.

Plasma cortisol concentration was highest shortly after surgery and then fell in all groups, these changes being similar to those of adrenaline and not corresponding to the increase in urinary nitrogen. However, cortisol concentrations in the two epidural groups were consistently and significantly lower than in the G group throughout the study. Since cortisol is the most potent single hormone to produce protein breakdown in extrahepatic tissues[11], the differences in cortisol levels between the G and the other groups may well have contributed to the difference in nitrogen loss, even though the postoperative concentrations were significantly lower than intra-operative levels.

Postoperative cortisol concentrations in the EM group were slightly lower than in the PE group. This result may indicate that postoperative sympathetic activity has little influence on cortisol levels, in contrast with the fact that sympathetic nervous impulses arising from the splanchnic nerves are largely responsible for the intra-operative cortisol response[13]. However, the reason for the slightly greater suppression of cortisol response in the EM group is not clear.

These results suggest that an increased sympathetic activity, induced by painful nociceptive and sympathetic nervous impulses, is responsible for the increased nitrogen loss, being mediated by glucagon and supported by cortisol. This may be consistent with the concept that sympathetic hyperactivity produces the insulin resistance in peripheral tissues[14] thus providing an underlying cause of protein breakdown[15].

This view seems to be in agreement with Wilmore *et al.*[16] who suggested that alterations in hypothalamic function due to injury, resulting in increased catecholamine elaboration, are fundamental in producing catabolic response to thermal injury.

Acknowledgements

The authors wish to thank Mr K. Satoh for his technical assistance and to Dr S. Ienaga for his critical reading of the manuscript.

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Paper accepted 27 November 1986

Announcement

Reviews

The Editorial Board of *The British Journal of Surgery* continues to invite review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium of £100. Potential authors seeking advice on the suitability of review topics are advised to contact: Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Glasgow G31 2EU, UK.

Leading articles

The Editors invite submission of signed leading articles to *The British Journal of Surgery*. These articles should be 600–1000 words in length, should address controversial topics of current interest and should be supported by selected key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium of £100 is payable on publication. Potential authors seeking advice on the suitability of topics are advised to contact: Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Glasgow G31 2EF, UK.

Surgical workshops

The Editors invite the submission of articles describing technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they can be accompanied by no more than two figures but should not carry supporting references. Articles submitted to the Surgical Workshop series may be subjected to external review and assessment by the Editorial Board before acceptance.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is likely to be high. Authors are advised to restrict such reports to a maximum of 500 words, to use no more than five references and to submit no more than one illustration.

Br. J. Surg. 1987, Vol. 74, May,
426–429

Value of nutritional parameters in the prediction of postoperative complications in elective gastrointestinal surgery

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The following nutritional parameters were assessed in 117 patients before major gastrointestinal surgery: percentage recent weight loss; percentage ideal body weight; tricipital skinfold; arm muscular area; grip strength dynamometry; serum albumin (ALB); serum transferrin (TFN); delayed hypersensitivity skin tests (DH); total lymphocyte count; prognostic nutritional index (PNI) and clinical assessment of malnutrition. Comparing the results in patients without complications ($n = 99$) *with those in patients with complications* ($n = 18$) *and the results in patients who survived* ($n = 109$) *with those who died* ($n = 8$), *we found that only ALB, DH, TFN and PNI showed significant differences in both comparisons. Correlations of complications with combined parameters was made by multiple linear regression analysis; a modified PNI (mPNI), including these three single variables, has emerged. Considering its risk values, the nutritional parameters showed the following sensitivity and specificity, respectively:* $ALB < 3{\cdot}2$ *g/dl (72 and 71 per cent), anergy (67 and 64 per cent),* $TFN < 205$ *mg/dl (67 and 55 per cent) and* $mPNI < 20$ *(72 and 70 per cent). Using Bayes' theorems, ALB, DH and calculated indices showed the same predictive capacity and we conclude that single or multiple association of nutritional parameters have no additive effect. To predict complications of nutritional origin it seems only necessary to consider ALB, taking into account the type of operation and the normal duration of postoperative hospital stay without oral intake.*

Keywords: Nutritional assessment, elective gastrointestinal surgery, prognostic nutritional index, surgical risk, pre-operative nutrition

Many postoperative complications are related to malnutrition but other variables may be present such as the underlying disease, associated organ failure or failures of surgical technique. Septic complications are frequent in digestive surgery, particularly in patients with malnutrition[1].

Müller *et al.*[2] showed the value of pre-operative parenteral feeding in patients with gastrointestinal carcinoma and Mullen *et al.*[3] advocated this nutritive support when a patient presents with a high risk prognostic nutritional index. However, the costs and complications of parenteral nutrition justify the study of nutritional parameters related to the surgical risk in order to select the patients in whom this support is useful. Many nutritional indicators have been proposed, such as grip strength dynamometry[4], serum albumin[5–7], serum transferrin[6], delayed hypersensitivity skin tests[8,9], total lymphocyte count[10], prognostic nutritional index[6] and clinical assessment of malnutrition[11,12]. Indeed, the nutritional status of a patient is dependent upon many factors and there are difficulties in their quantification[7]. The different predictive values of the indicators reported by several authors led us to undertake the present prospective study in which we tried to find a practical prognostic index.

Patients and methods

Patients

During a 10-month period 117 consecutive patients, admitted to the Department of Clinical Surgery at the Coimbra University Hospital for elective major gastrointestinal surgery, were studied. The group consisted of 69 men and 48 women, with ages ranging from 20 to 90 years (mean age $58{\cdot}9 \pm 15{\cdot}6$). Malignant disease was diagnosed in 64 patients (oesophagus 7, stomach 20, large bowel 15, pancreas 6, biliary tree and liver 5, other 11) and benign conditions in 53 patients (peptic ulcer 12, chronic and acute cholecystitis 11, choledocholithiasis 8, biliary pancreatitis 9, other 13). All the patients were operated on by four surgeons using similar surgical criteria. In 43 patients the tumour was removed by formal resection and in 21 patients a palliative procedure was carried out. Pre-operative clinical sepsis was present in 13 patients: 7 with cholangitis, 2 with acute cholecystitis, 2 with abdominal abscess and small bowel fistula, 1 with pancreatic abscess and 1 with subhepatic abscess secondary to perforated duodenal ulcer. No patient had received pre-operative parenteral nutrition and 16 had postoperative nutritional support determined by the occurrence of complications. The patients with contaminated operations received prophylactic antibiotics which were maintained postoperatively in all dirty operations.

Nutritional assessment

Two to three days before surgery the following parameters were assessed: anthropometric, biochemical, immunological, multifactorial indices and clinical assessment.

The percentage of ideal body weight was calculated by the formula: percentage ideal weight = actual weight/ideal weight × 100. The ideal weight was based on the 1959 Metropolitan Life Insurance Table[13], as there are no adequate Portuguese tables. The percentage of recent weight loss was determined from the formula: percentage weight loss = usual weight − actual weight/usual weight × 100. Triceps skinfold (TSF) was measured by the standard technique[10] and arm muscular area (AMA) was evaluated using the relationship: $AMA = (\text{mid-arm circumference} - \pi TSF)^2/4\pi$ (Reference 14). Grip strength of dominant hand was measured using a dynamometer for adults, considering the mean value of three maximal squeezes with readings on the dial in kilograms. Serum albumin (ALB) was measured by a colorimetric method. Serum transferrin (TFN) was indirectly calculated by total iron binding capacity (TIBC) using the formula: $TFN = 26{\cdot}8 + 0{\cdot}76\ (TIBC)$,

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established by our Hospital Laboratory[15]. Delayed hypersensitivity skin tests (DH) with five antigens (purified protein derivative, *Candida*, trichophytin, mumps skin test antigen and streptokinase–streptodornase) were performed with methods and dilutions as recommended by Meakins *et al.*[9]. Injections and induration measurements were made by one of us (J.F.M.S.L.). A positive reaction with each antigen was defined as ≥ 5 mm induration at 24 or 48 h. A normal delayed hypersensitivity response required two or more positive reactions and anergy was defined as no reaction to any of the five antigens or reaction to only one of the antigens.

Prognostic nutritional index (PNI) described by Buzby *et al.*[1] was calculated with the formula: $\mathrm{PNI} = 158 - 16{\cdot}6\ (\mathrm{ALB}) - 0{\cdot}78\ (\mathrm{TSF}) - 0{\cdot}20\ (\mathrm{TFN}) - 5{\cdot}8\ (\mathrm{DH})$, in which DH is related with the reactivity to any of the three recall antigens (mumps, streptokinase–streptodornase, *Candida*) graded as 0 (non-reactive), 1 (<5 mm induration) or 2 (≥ 5 mm induration).

Clinical assessment of malnutrition was judged by one of us (J.F.M.S.L.) before knowing the objective and laboratorial tests previously described. Subjective assessment was based on history of weight loss, anorexia, vomiting or diarrhoea and objective findings of muscle wasting, loss of subcutaneous fat, glossitis, cheilosis and oedema. The patients were scored on one of the following: no malnutrition, mild, moderate or severe malnutrition. The cases scored with moderate and severe malnutrition were considered to have clinical malnutrition.

Postoperative complications

Each patient was followed until discharged from hospital or eventual death. In this study the nutritional parameters of the patient without postoperative complications or with minor complications, such as superficial phlebitis, minor wound infection or wound haematoma that had no impact on expected length of stay, were compared with those with major complications. Objective criteria were established for diagnosing each major complication: septicaemia required a positive blood culture; intra-abdominal sepsis was diagnosed when a purulent collection required drainage; fistula and pneumonia needed radiological documentation; wound infection required a positive bacterial culture; wound dehiscence requiring re-operation; respiratory failure was diagnosed when the patient needed assisted ventilation; heart failure was judged from clinical and radiological criteria; pulmonary emboli were demonstrated by lung scintigraphy or postmortem examination; cerebrovascular accident was diagnosed clinically and renal failure was confirmed when the patient needed dialysis.

When more than one complication occurred in a single patient only the most severe was considered. Patients who died during hospitalization were included in the group with major complications.

Statistical methods

Differences between means were compared by the Student's *t* test and differences between frequencies were calculated by χ^2 test with Yates' correction. Multiple linear regression analysis relating nutritional parameters to complications were performed by ANOVA[16].

Sensitivity and specificity of nutritional parameters were evaluated considering cut-off points and risk values. The cut-off points of the analysed variables were considered as the mid points between the centroids of the groups with and without complications[17]. Other cut-off points were also tested but the best sensitivity–specificity results were obtained with the method of analysis described. Bayes' theorem was used to calculate predictive probability of postoperative complications for each risk indicator[18].

Results

The postoperative course was uncomplicated in 90 patients (76·9 per cent), minor complications occurred in 9 patients (7·7 per cent) and major complications developed in 18 patients (15·4 per cent) and of these 8 died. Major complications were related to sepsis in 6 patients, including septicaemia (2), pneumonia (2) and intra-abdominal abscess (2). Non-septic major complications occurred in 12 patients, including wound dehiscence (2), renal failure associated with peritoneal carcinosis (2), respiratory failure (1), pancreatic pseudocyst (1), biliary fistula (1), intestinal obstruction (1), enteric fistula (1), multiple organ failure (1), cerebrovascular accident (1) and hepatorenal failure (1). The patients who died were significantly older (*Table 1*) and there was no significant higher morbidity and mortality in patients who presented with malignant disease. In this group of patients in whom the tumour was removed morbidity and mortality were respectively 13·9 per cent (6/43) and 2·3 per cent (1/43). When only a palliative procedure was performed both morbidity and mortality values were higher, respectively 33·3 per cent (7/21) ($P<0{\cdot}10$) and 28·6 per cent (6/21) ($P<0{\cdot}001$). Complications after resection of the tumour occurred in six patients who underwent major operations, i.e. oesophagogastric resection (2), total and subtotal gastrectomy (2) and abdominoperineal resection of the rectum (2). Postoperative complications which occurred in five patients with benign diseases were related to drainage of pancreatic abscess, resection of small bowel associated with abscess and internal fistula, resection of hydatid cyst of the liver, partial gastrectomy for gastric ulcer penetrating to the pancreas and cholecystectomy for biliary pancreatitis.

The values of nutritional parameters of the group of patients with postoperative complications were compared with those of the group who recovered without complications (*Table 1*). Furthermore, the values of the group of patients who survived were also compared with those who died, as is also shown in *Table 1*. The mean values of ALB, TFN, PNI and the incidence of anergy showed significant differences in both comparisons. The mean values of percentage weight loss, TSF and grip strength dynamometry showed significant differences only on a single comparison. The mean values of percentage ideal weight, AMA, total lymphocyte count and the incidence of clinical

Table 1 *Nutritional parameters in four groups of patients**

	Group 1 99 patients without complications	Group 2 18 patients with complications	*P* 1 *versus* 2	Group A 109 patients alive	Group B 8 patients dead	*P* A *versus* B
Age (years)	58·5±15	61·3±18	n.s.	58·3±16	68·5±4	<0.01
Malignant disease (no. of cases)	51	13	n.s.	57	7	n.s.
Percentage ideal weight	96·8±16·6	89·2±17·6	n.s.	96·0±16·7	90·4±20·2	n.s.
Percentage weight loss	6·9±8·1	9·4±6·1	n.s.	6·9±7·9	11·9±5·9	<0·05
TSF (mm)	9·6±5·7	6·8±3·0	<0·01	9·4±5·5	6·6±4·1	n.s.
AMA (cm^2)	37·7±10·8	37·6±11·8	n.s.	37·7±10·9	37±10·9	n.s.
Grip strength (kg)	55·2±24·6	49±29·6	n.s.	55·4±25·2	38·4±22·8	<0·05
ALB (g/100 ml)	3·46±0·64	2·96±0·81	<0·01	3·42±0·64	2·69±0·73	<0·01
TFN (mg/100 ml)	228±59	195±45	<0·05	226±59	186±42	<0·05
Total lymphocyte count (no./mm^3)	1950±840	2030±639	n.s.	1960±810	2030±760	n.s.
Anergy (no. of cases)	35	12	<0·01	41	6	<0·05
PNI (Buzby[1])	34·4±25	58·9±27	<0·01	36±26	67·5±25	<0·01
Clinical malnutrition (no. of cases)	24	8	n.s.	28	4	n.s.

* Comparison of nutritional parameters between Group 1 and Group 2 and Group A and Group B; Values are means±s.d.; TSF, triceps skin fold; AMA, arm muscular area; ALB, serum albumin; TFN, serum transferrin; n.s., not significant

Table 2 *Sensitivity and specificity of nutritional tests considering its risk values related with postoperative complications*

	Selected cut-off	Sensitivity (%)	Specificity (%)	Source
Albumin	<3·2 g/100 ml	72	71	present series
	<3·5 g/100 ml	43	66	Detsky *et al.*[12]
Transferrin	<205 mg/100 ml	67	55	present series
	<150 mg/100 ml	57	78	Detsky *et al.*[12]
Delayed hypersensitivity	anergy	67	64	present series
	anergy	52	83	Christou *et al.*[8]
PNI (Buzby)	>40 points	78	58	present series
	>40 points	88	45	Buzby *et al.*[1]
mPNI	>20 points	72	70	present series
Clinical assessment	malnutrition	55	75	present series
		82	72	Detsky *et al.*[12]

Table 3 *Probability of postoperative complications related with normal and risk values of nutritional tests**

	Cut-off selecting high surgical risk	Probability of complications (%)	
		With normal values	With risk values
Albumin	<3·2 g/100 ml	6·5	30·5
Transferrin	<205 mg/100 ml	9·6	20·8
Delayed hypersensitivity	anergy	8·5	32·3
mPNI	>20 points	6·6	29·7
I (ALB+TFN)	>18 points	6·6	29·5
I (ALB+DH)	>18·5 points	7·0	27·2
I (TFN+DH)	>18 points	7·4	29·6
PNI (Buzby)	>40 points	6·4	24·2

* Using Bayes' theorem

malnutrition showed no significant differences on either comparison.

The incidence of anergy in patients with malignant pathology was 50 per cent (32/64) and in those who presented benign conditions was 28·3 per cent (15/53) ($P<0·05$).

Multiple linear regression analysis was applied to three variables (ALB, TFN, DH) that previously showed good correlation with major complications and mortality and generated the following indices:

$$\mathrm{I(ALB, TFN, DH)} = 60{\cdot}3 - 7{\cdot}5\,\mathrm{(ALB)} - 0{\cdot}006\,\mathrm{(TFN)} - 8{\cdot}8\,\mathrm{(DH)} \quad (F=3{\cdot}85, P<0{\cdot}05)$$

$$\mathrm{I(ALB, TFN)} = 66{\cdot}4 - 10{\cdot}6\mathrm{(ALB)} - 0{\cdot}07\mathrm{(TFN)} \quad (F=5{\cdot}08, P<0{\cdot}01)$$

$$\mathrm{I(ALB, DH)} = 55 - 10{\cdot}2\mathrm{(ALB)} - 9\mathrm{(DH)} \quad (F=4{\cdot}99, P<0{\cdot}05)$$

$$\mathrm{I(TFN, DH)} = 43 - 0{\cdot}09\mathrm{(TFN)} - 13{\cdot}4\mathrm{(DH)} \quad (F=4.91, P<0{\cdot}05)$$

in which DH is the cutaneous response to five antigens graded as 1 for normal and 0 for anergy. The index I (ALB, TFN, DH) was considered as a modified prognostic nutritional index (mPNI) and the retrospective application of this index to the present series showed the following results: in the group of patients without postoperative complications the mPNI was 15 ± 10 and in the group of patients with postoperative complications the mPNI was 24 ± 11 ($P<0·008$); in the group of patients who recovered from the operation mPNI was 16 ± 10 and in the group of patients who died mPNI was 28 ± 10 ($P<0·001$).

The selected cut-off values were: ALB = 3·2 g/100 ml, TFN = 205 mg/100 ml; and mPNI = 20 points. Sensitivity and specificity of these nutritional tests and of PNI, DH and clinical assessment of malnutrition are shown in *Table 2*, together with the published results of other series. In the present series ALB was found to have the best combination of sensitivity (72 per cent) and specificity (71 per cent).

Using Bayes' theorem (*Table 3*) the calculated probability of the development of major complications when the nutritional parameters presented risk values was between 32·3 and 20·8 per cent. When normal values were found the probability of postoperative complications was between 9·6 and 6·4 per cent. The global results of the indicators studied were similar, with the exception of TFN which showed the lowest predictive values.

Discussion

This study confirms that the most relevant indicators of malnutrition are related to major postoperative complications as has also been demonstrated by other investigators[1,2,12,19,20]. Nevertheless, other non-nutritional factors can affect the postoperative course, the relative importance of each in contributing to morbidity and mortality being difficult to analyse.

Patients with unresectable tumours, although submitted to small palliative procedures, had a higher incidence of complications. This shows the stronger influence of the underlying disease and associated malnutrition over the magnitude of the operation. On the other hand, the postoperative complications observed in patients with resectable tumours occurred following major operations with long hospital stay without oral intake. In patients with benign conditions, complications were related to pre-existing sepsis and complex technical procedures.

Malnutrition is associated with protein depletion, lower body cell mass and expansion of the extracellular fluid compartment which results in oedema. This excess fluid can lead to respiratory or cardiac failure[21]. In this study major complications were related to failure of vital organs in 27·7 per cent (5/18) of the patients, including 4 with advanced malignancies. Thus, these results suggest the need for a careful pre-operative assessment of vital organs as an independent variable leading to complications, as has recently been reported[20].

Faulty surgical technique, as another source of complications, was thought not to affect greatly the present results. However, it should be accepted that this is a difficult variable to assess.

Some of the nutritional parameters analysed in this study were found to have no clinical role. The classic anthropometric measurements, according to other studies[6,7,20], have low predictive capacity. The value of grip strength dynamometry as a prognostic index of serious postoperative complications was not confirmed in our study. We think that other non-nutritional factors can affect the value of this indicator, such as, age, sex and occupation. Clinical assessment of malnutrition through history and physical examination was found to have the best combination of sensitivity and specificity[11,12,22], but we did not confirm these findings and our results favour the view that malnourished patients cannot be adequately identified by clinical examination alone[23].

Other nutritional tests have been shown to select a high risk population. ALB was found to be the best single indicator of surgical risk, as reported[6,19], with quick, easy and accurate assessment, free from dependence on the skill of the operator. It should be emphasized that rapid fluctuations in ALB can be the result of variations in the extracellular fluid compartment without reflecting changes in nutritional status. This is likely to occur in patients undergoing emergency surgery and during the postoperative period[21].

TFN is also a valuable indicator of risk but has not shown higher predictive capacity than ALB[5,6,19], in spite of its shorter half-life that could better reflect acute malnutrition[10]. This discrepancy may be explained by the error found on indirect calculation of TFN by TIBC[15]. The values of skin tests to predict postoperative complications have shown contradictory results[1,8,9,24,25]. Many factors other than malnutrition can modify skin reactivity to allergens, such as age, underlying disease, technical problems or drug treatments[26]. Our results confirmed that cutaneous anergy is an indicator of surgical risk but without added value over other simpler nutritional markers.

Anergy was more frequent in patients with malignancies, yet a significant increase of complications was not found in these patients. These results suggest that anergy is related to surgical risk regardless of the underlying disease. The high incidence of anergy found in our patients when compared with that found by others[9,24] may be explained by the significant number of cases with advanced malignancies and sepsis.

Considering the global results of sensitivity and specificity of the nutritional tests in *Table 2* we conclude that all have limited predictive capacity. Different published results, reported by others[1,8,12] can probably be explained by heterogeneous clinical populations, limited number of cases or different incidence of non-nutritional associated complications. We have attempted to provide a prognostic nutritional index by using a combination of the best nutritional parameters but have failed to show any benefit for it. Sensitivity, specificity and Bayes probability analysis demonstrated that single or multiple associations of nutritional markers have no extra predictive value. PNI of Buzby *et al.*[1] applied to our patients also showed that its best predictive capacity remains to be proven, as has also been reported[20,27].

Thus, we suggest that, for practical purposes, when planning major gastrointestinal surgery, only the ALB level needs to be considered, and if lower than 3·2 g/100 ml, there will be a fivefold increased risk of serious postoperative complications.

Acknowledgements

The authors are grateful for the assistance of their colleagues at the Department of Clinical Surgery and at the Laboratory of Haematology of Coimbra University Hospital.

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Paper accepted 12 December 1986

Br. J. Surg. 1987, Vol. 74, May,
430–435

Arterial healing in the dog after intraluminal delivery of pulsed Nd–YAG laser energy

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The application of laser energy to percutaneous recanalization of diseased blood vessels is of interest to vascular surgeons and radiologists. We have examined the effect of pulsed infrared light from a 100 μs pulsed Nd–YAG laser on the dog aorta in order to determine the dose response, perforation thresholds and healing properties in vascular tissue. We used 100 μs pulses of 0·5 J energy at 10 Hz repetition rate via a 400 μm optical fibre to make 205 craters in 10 dogs at total energies of 5–25 J. The perforation threshold was 15 J in six animals and 20 J in four. The dose response was linear at 10 μm tissue vaporized per Joule delivered. Animals were killed immediately and at intervals of 24 h, 4, 7 and 10 days, 2, 3 and 6 weeks, and 3 and 6 months. Material was retrieved for histology and examined by light and scanning electron microscopy. The tissue exhibited features of laser damage that were less marked than those seen with continuous wave lasers; there was less heat damage surrounding the craters which healed well, even after perforation. This laser is likely to be suitable for human laser angioplasty provided the energy is given in increments of 15 J or less.

Keywords: Laser angioplasty, pulsed Nd–YAG laser, arterial healing

The use of laser light to vaporize atheromatous tissue and thus provide a new treatment for obstructive arterial disease is under investigation[1–3]. It is possible to introduce laser light percutaneously via an optical fibre to areas of atheroma, either with the aid of an angioscope or with X-ray screening. Vaporization of atheromatous material with subsequent recanalization, either instead of or as an adjunct to established techniques of revascularization, might make hitherto inoperable disease in the smaller vessels of the leg amenable to treatment. Various laser wavelengths ranging from the mid-infrared to the far ultraviolet have been considered for this purpose, with varying results[4,5]. The carbon dioxide laser (10·6 μm, mid-infrared) cannot be used percutaneously at the moment, as the availability of suitable optical fibre for its transmission is limited[6]. The excimer laser (193, 249, 308 and 351 nm, ultraviolet) is in the early stages of clinical development. The shorter wavelengths will not pass along currently available fibres; the longer wavelengths (308 and 351 nm) can be carried by quartz fibres but the high peak pulse power of the laser tends to shatter the proximal end of the fibre, preventing adequate energy deposition at the distal end[7]. In addition, the possible genetic effects on vascular tissue of these short wavelengths have yet to be assessed[8]. The presently available flashlamp excited pulsed dye lasers (variable wavelengths in the visible range) are in the early stages of investigation for angioplasty. This leaves three lasers being considered for clinical cardiovascular use: the continuous wave argon ion laser (488 and 514·5 nm, blue-green) and the continuous wave and pulsed Nd–YAG (neodymium–yttrium aluminium garnet) lasers (1064 nm, near infrared). The output from all of these can be transmitted down a fibre with enough energy and power to ablate vascular tissue.

Clinical work has already started with the continuous wave devices. The argon laser has been used on coronary arteries at open operation[9] and both the argon and the continuous wave Nd–YAG lasers have been used percutaneously in the peripheral circulation, but experience is so far limited[10,11]. As a variation on laser vaporization, the argon laser can be used to heat a metal olive at the fibre tip, which then bores a hole through the obstructed artery. Successful recanalization of peripheral and coronary human blood vessels in conjunction with balloon angioplasty has recently been reported[12,13].

It has been suggested that the use of a pulsed laser limits tissue damage beyond the area of vaporization[14]. We describe the effect of 100 μs pulsed Nd–YAG laser radiation on living vascular tissue, the pulse length being the shortest commensurate with both reliable fibre transmission and effective tissue interaction. In a laser angioplasty some light is bound to fall on surrounding normal endothelium, and this study is designed to examine both the effects of this type of laser energy or normal canine vessel wall, and the subsequent healing process.

Materials and methods

The laser used in these experiments was a JK System 2000, 100 μs pulsed Nd–YAG laser built by JK Lasers of Rugby, UK. The Nd–YAG crystal is optically pumped by xenon flashtubes energized from high storage capacitors to give energies of up to 0·5 J per pulse (measured at the fibretip) with an output wavelength of 1064 nm. At a repetition rate of 10 Hz this gives an average output of 5 W measured at the fibretip. Each pulse is 100 μs in duration; because the laser is firing for only 1 ms out of every second the peak pulse power is therefore 5000 W. The laser beam was focused onto the end of a 0·4 mm diameter flexible quartz optical fibre of cross sectional area 0·13 mm^2; the peak power at the fibretip per unit area is just under 400 MW cm^{-2}. Because the infrared output of the laser is invisible the beam is aligned using a red helium–neon laser focused through the cavity and down the fibre in the same way as the main laser. The optical quality of the fibre tip was checked using this beam. The output of the laser was measured at the fibretip using a Scientech 38-0401 volume absorbing calorimeter.

Ten greyhound dogs (weight 25·1 kg ± 2·7 s.d.) were anaesthetized with methohexitone and oxygen/halothane following which the abdominal aorta was dissected free from the retroperitoneal tissues over a length of 10 cm. A silk purse-string suture was placed in the adventitia and a 21 gauge needle introduced into the lumen, its position being confirmed by backflow. The 0·4 mm internal diameter optical fibre was passed down the needle until it met the intimal surface of the posterior wall of the aorta at right angles. Care was taken to avoid the ostia of the lumbar arteries. Five separate exposures at a given energy level were then made, the fibre being repositioned after each exposure. The needle

Table 1 *Perforation rates in dog aorta exposed to increasing doses of pulsed Nd–YAG radiation*

Energy (J)	Acute vessel perforation
5	0/40
10	0/40
15	25/40
20	40/40
25	10/10

and fibre were then withdrawn and the purse string suture tied to stop bleeding and provide a marker when examining the tissue later. The needle and fibre were then reintroduced through a fresh suture at a different site and five new craters made at a different energy dose. Tissue exposure parameters were based on those defined when exposing human cadaver material to energy from the same laser under blood[15]; in all cases the laser was set at a repetition rate of 10 Hz, 0·5 J per pulse measured at the distal end of the fibre before each exposure. Exposures of 1–5 s were made, giving an energy dose of 5–25 J. The outside surface of the aorta was examined for evidence of perforation; when this occurred the bleeding was controlled by pressure. Any perforations were thus allowed to seal spontaneously without suture.

The fibre was deliberately introduced to the tissue at right angles to simulate the worst possible case of accidental injury to normal tissue; we have shown in cadaver experiments[15] that such damage is mitigated by decreasing the angle of incidence of the fibre to the tissue.

Five craters at each of five energy levels (5–25 J) were made in the first dog to establish perforation thresholds; subsequently five craters at each of four energy levels (5–20 J) were made in the remaining nine dogs. The results outlined below are therefore based on measurement of 205 craters.

All dogs were exposed to laser light in the same way and then killed at survival times of: 0, 1, 4, 7 and 10 days; 2, 3 and 6 weeks; and 3 and 6 months to give a sequential picture of tissue healing. The retrieved tissue was examined histologically; the target areas could readily be identified using the marker sutures even in the absence of obvious macroscopic damage. The depths of visible craters in the aorta of the first animal, killed immediately after exposure, were measured to an accuracy of ±5 μm using a Prior micromanipulator. Tissue was fixed in formalin and embedded in wax; 4 μm sections were cut and stained using haematoxylin and eosin stains. Selected animals were treated with a perfusion fixation technique using buffered glutaraldehyde and the endothelium examined by scanning electron microscopy after critical point drying and coating with a thin layer of gold.

All exposed tissue was satisfactorily retrieved and examined. No dogs were lost either peroperatively or during subsequent care.

Results

Macroscopic findings

Acute perforation threshold. With the 80 energy deliveries of ≤10 J, there was no perforation of the aortic wall. However with the 40 energy deliveries of 15 J, there were 25 vessel perforations, and with energy deliveries of ≥20 J, all vessels were perforated (*Table 1*). The perforation threshold was therefore 15 J in six animals and 20 J in four. All perforations sealed spontaneously within 5 min of occurrence. There was no evidence of delayed perforation at death.

Dose–response. Macroscopic examination in the first animal immediately after laser damage revealed discrete craters in the vessel wall, increasing in depth with increasing applied energy. Crater depths were measured and the results are shown in *Figure 1*. Between 5 and 25 J, there is a linear 'dose–response' relationship between energy delivered and crater depth produced, with a slope of 10 μm increase in penetration depth per Joule increase in delivered energy. However this slope does not pass through the origin, and the initial 'dose' of only 5 J penetrates 235 μm into the vessel wall, representing an initial slope of 47 μm penetration per Joule of energy delivered. This finding is related to pulse energy and is discussed below. None of the acute craters examined contained blood clot.

Healing profile. By 24 h all the craters contained thrombus but this did not extend into the lumen of the aorta. At 4 days the craters were still full of thrombus but were less distinct and by 7 days healing was evident. By 14 days all that remained were a few poorly defined pits in the vessel wall, completely healed over, and beyond this time no intimal damage could be seen with the dissecting microscope.

Microscopic findings

Histology of the acute lesions revealed well demarcated craters with surrounding tissue damage limited to a thin (20 μm) rim of tissue coagulation at the base of the crater, not related to energy dose. As the energy level increased the craters became progressively deeper until the perforation threshold was reached. There were erythrocytes adherent to the crater floors; lateral to the crater wall there was compression injury which was less pronounced than that deep to the crater and was associated with deviation of medial smooth muscle fibre lie towards the crater floor (*Figure 2*). In perforated lesions, there was an adventitial haematoma extending laterally by up to 2 mm, as well as a small amount of medial intramural haematoma (*Figure 3*). At 24 h, craters (whether or not perforated) were incompletely filled with a coagulum of blood clot and medial debris. The subjacent damage extended through the vessel wall in the shape of an inverted cone, the damage becoming broader from intima to adventitia. Medial intramural haemorrhage was more pronounced than that seen initially and there was no cellular infiltration.

From 4 to 7 days, the craters and perforations were completely filled with thrombus, around which there was minimal white cell infiltration. New endothelial cells were beginning to cover the thrombus. Most marked was the inverted cone of subjacent damage extending deep and lateral to the craters. This overlapped with similar subjacent damage caused by the neighbouring laser lesions, sited 2 mm distant along the aortic wall. For craters which had extended only 300 μm into the media this subjacent damage extended through to the adventitia, a total distance of 1 mm. Overall, in the region of the laser lesions, the vessel was thinned by some 50 per cent, due mainly to medial thinning associated with absent nuclei representing muscle cell death.

At 10 days there was definite evidence of healing. The thrombus plug, and the medial and adventitial haematomas were becoming organized with a more marked cellular infiltrate of white cells and fibroblasts, and overall vessel wall thinning was less pronounced. From 2 to 3 weeks the intima was almost completely endothelialized, with thickening of the neo-intima;

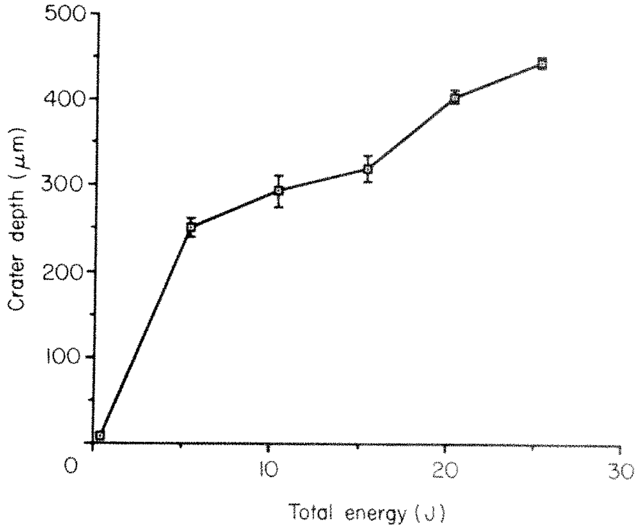

Figure 1 *The acute dose–response to pulsed Nd–YAG laser light in the dog. The crater depth recorded at 20 and 25 J total energy dose represents perforation into the adventitia. Mean depth of 5 craters + s.e.m. per point*

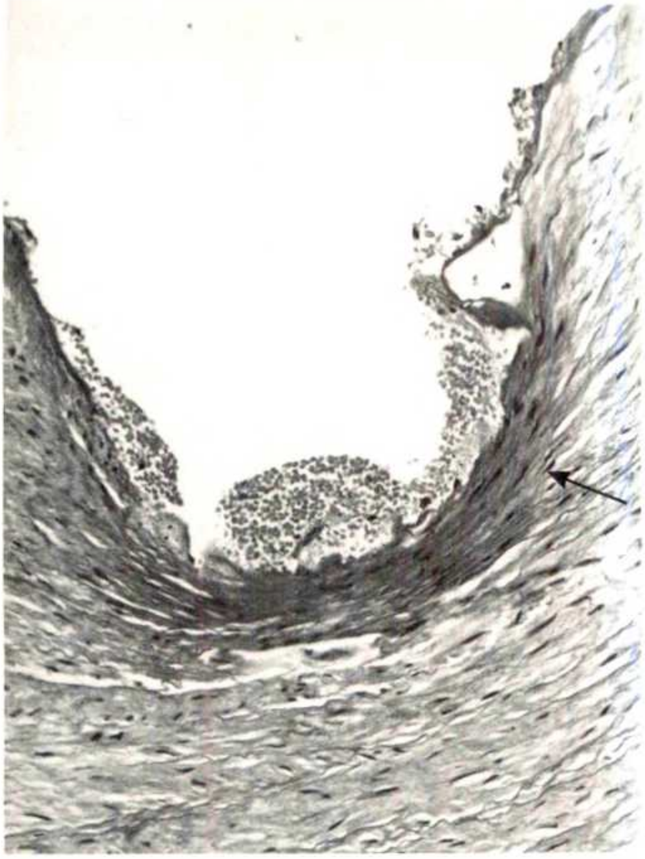

Figure 2 *An acute crater produced in the dog aorta by 15 J laser energy (haematoxylin and eosin, medium power). Tissue has been vaporized and the edges of the crater are well-demarcated showing a thin rim of coagulation. A small amount of thrombus is seen in the crater floor. There is deviation of the smooth muscle fibre lie (arrow)*

300 μm compared with the 50 μm thickness of adjacent undamaged intima with which it made a smooth junction. The adventital and medial haematomas were becoming resorbed and replaced with fibroblasts amongst which regenerating myocytes and their nuclei could be seen, though deviation of medial muscle fibre lie and both adventital and medial thinning were still evident (*Figure 4*).

By 6 weeks haematomas had resorbed and craters could no longer be defined histologically, there being extensive cellular regeneration throughout the damaged media, with no deviation of muscle fibre lie (*Figure 5*). There was some overall thickening of the vessel wall in the damaged area, this being due to the neo-intimal thickening which itself did not encroach upon the vessel lumen, but more than compensated for the residual medial thinning. In the healing area the thickness of the intima was 200 μm, of the media 650 μm and of the adventitia 50 μm. The respective values for adjacent undamaged vessel wall were 50, 550 and 220 μm.

At 12 weeks the full thickness damage had become almost completely repaired, and the neo-intimal thickening was less pronounced (100 μm). In some areas there was still some overall vessel wall thickening due mainly to enlargement of the adventitia which may simply represent healed haematoma. By 6 months there was little evidence of vessel wall damage; in particular there were no late aneurysms or strictures. The medial muscle cell disposition exhibited some disruption but cell nuclei had reappeared and the cells themselves appeared healthy.

Scanning electron microscopy

Scanning of fresh craters in animals killed immediately showed craters in the endothelium, slightly irregular in outline, with red blood cells adherent to the base and sides. The surrounding endothelium appeared to have suffered some tearing and lifting; by 24 h there was evidence of cell death up to a distance of 100 μm from the crater edges. At 7 days there was clear evidence of regeneration of the intima although elevated intima could still be seen around the crater edges. There was a fibrin plug inside the crater; red cells within this plug could clearly be seen in the crater floor. Dividing cells could be demonstrated at the crater edge (*Figure 6*). At 14 days a new layer of intimal cells had completely covered the craters and, from the point of view of the endothelium, healing was complete.

Discussion

The first lasers to be invented were pulsed, and many industrial processes, particularly cutting and welding, continue to rely on pulsed output from CO_2 and Nd–YAG lasers. Early experience with pulsed lasers in medicine was generally unhappy, largely because of the disruptive effects of the very high power pulses produced by these industrial devices[16]. Continuous wave lasers are easier to manage and have been successfully applied in a limited number of clinical fields[17,18]. Experimental studies with continuous wave lasers for angioplasty, though initially promising, revealed an unacceptable rate of vessel perforation, due mainly to the subjacent thermal damage which they produce[19]. This was particularly the case with the Nd–YAG laser[20]. The risk of lesser degrees of damage such as stricture or aneurysm formation[21], has hindered the clinical application of continuous wave lasers to angioplasty, and attention is again turning to pulsed lasers as being possibly safer.

As far as tissue interactions are concerned, the microsecond-pulsed Nd–YAG laser is an entirely different instrument from continuous devices. The average power emitted from a pulsed

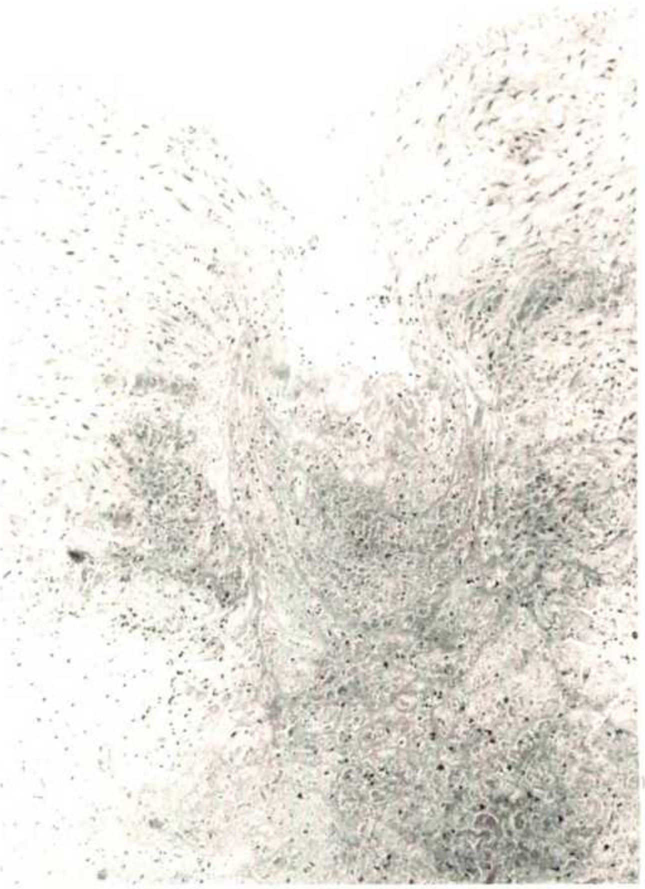

Figure 3 *Acute crater from 25 J laser energy (haematoxylin and eosin, low power). There is a deliberate perforation of the vessel wall. Little subjacent laser damage can be seen around the crater but there is marked intramural haemorrhage as well as a large adventitial haematoma extending into the surrounding tissue*

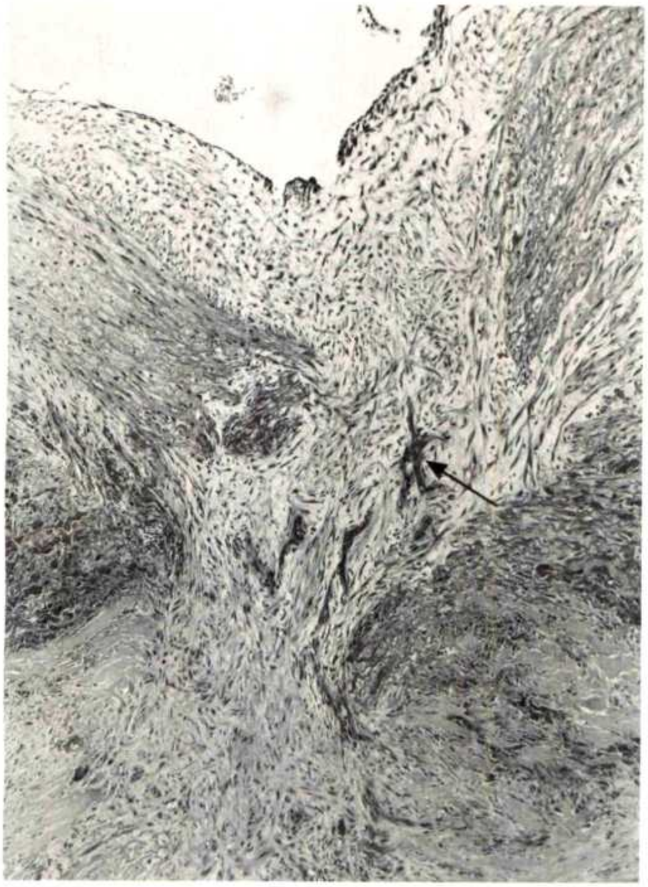

Figure 4 *Crater from 25 J, day 10 (haematoxylin and eosin, medium power). This deliberate perforation has now filled with a fibrous plug and the surface has become covered with a thickened neo-intima. Medial disruption remains obvious and there are regenerating myocytes within the fibrin plug (arrow)*

laser is the same as that from a continuous wave laser, but it is applied in short pulses of very high power. It was shown in 1965 that the tissue damage surrounding a crater vaporized in pig skin using a 20 ns pulsed ruby laser was less than that seen with a microsecond-pulsed laser of the same wavelength[22]. More recently it has been shown qualitatively that the pulsed CO_2 laser vaporizes precise craters in tissue whereas the equivalent continuous wave laser leaves surrounding subjacent thermal tissue damage[14]. We have demonstrated that this is also true of Nd–YAG laser energy which can penetrate up to 6 mm in tissue (*Figure 7*)[23]. The reasons for this lie in the rate of heat transfer and its dissipation in tissue. Giving large amounts of energy in short pulses allows the tissue adjacent to the immediately irradiated zone time to cool off between pulses, thus preventing excessive thermal damage[22]. It can be seen from this that the pulse repetition rate is as important as the pulse length in this respect. Living tissue can withstand heating up to a point; the shorter the exposure time, the higher the temperature that can be tolerated[25]. With a pulsed laser tissue can probably be heated up to a temperature of 80°C for the 0·1 ms for which the laser is applied, without irreversible damage. In addition, a high energy density will be more likely to induce a phase change (i.e. vaporization) in the exposed tissue; such a change requires much energy which goes into the vaporized particles leaving the surface, with little heat remaining to cause subjacent damage. Limiting damage in this way has potential advantages in laser angioplasty; it may reduce the incidence of perforation (given that any laser will perforate a vessel if the energy dose is high enough) and perhaps also the likelihood of aneurysmal change in a weakened wall, or of medial fibrosis leading to a stricture. There is a minimum threshold energy per pulse for vaporization of tissue; our observations suggest that this is about 0·1 J/pulse delivered down a fibre of 0·4 mm diameter. For this reason the acute dose response of the aorta at 0·5 J/pulse shown in *Figure 1* fails to pass through the zero point, since the laser is operating well above the vaporization threshold.

The shorter the pulse duration and the higher the peak pulse power, the easier it is to limit the extent of subjacent thermal damage[24]. Unfortunately it also becomes more difficult to transmit such pulses down an optical fibre since they tend to shatter the proximal end[26]. Lasers (such as the excimer) which give virtually no subjacent thermal damage cannot yet be conveniently transmitted fibre-optically, at least not at the combination of wavelength, energy and power required for ablation. The energy parameters of the laser used in this study were chosen so that they could be transmitted fibre-optically, yet still confer some of the advantages of the short pulse duration, high peak power lasers.

Vascular healing following the *in vivo* delivery of argon laser energy has been shown to take place within 6 weeks in normal dogs and atheromatous monkeys with repair of laser craters and re-endothelialization[27]. There has been one report of late aneurysm formation following *in vivo* delivery of argon laser energy in atheromatous rabbits[21]. One study shows that, although there is some limited acute subjacent damage, vascular healing following delivery of microsecond pulsed Nd–YAG laser energy is at least as complete as that following continuous wave argon laser energy delivery in the hands of other workers. The features of vascular healing are the same as those seen following needle puncture of the carotid artery, well described by Crawford[28]. The similarity between healing after perforation using the laser or the needle is striking; there is the same fibrin plug, the same failure of the elastic lamina to regenerate

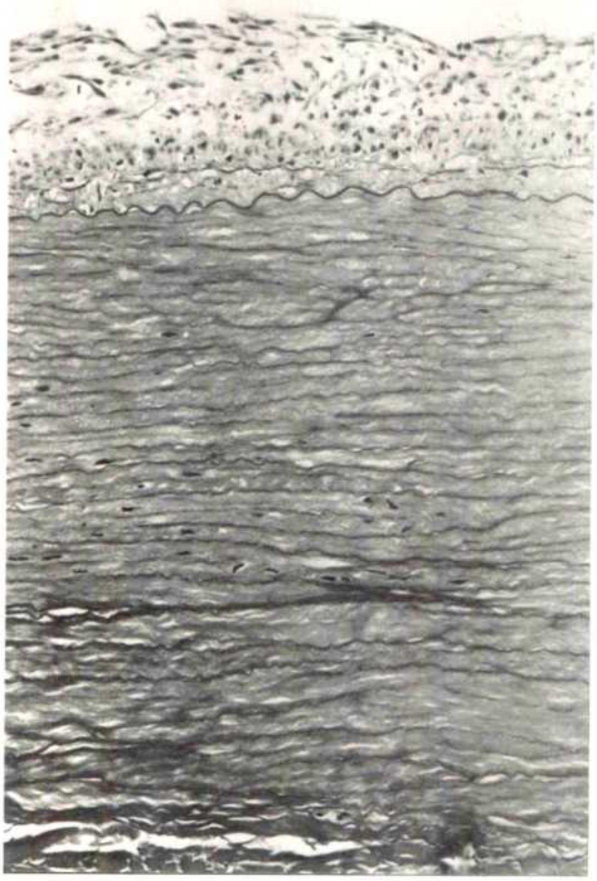

Figure 5 *Crater from 15 J, 6 weeks (haematoxylin and eosin, medium power). The damaged aorta has largely recovered but smooth muscle cell nuclei are still reduced in numbers. The neo-intima remains thickened and there is residual disruption of the elastic layers*

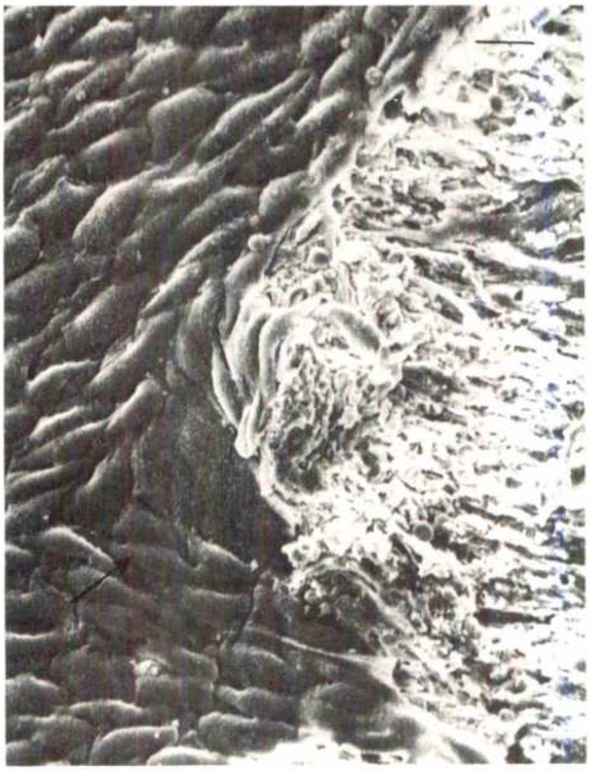

Figure 6 *High power SEM of crater, scale cursor 10 µm. The advancing edge of healing endothelium (left) is seen encroaching on the exposed medial surface (right). Cells can be seen actively dividing (arrow)*

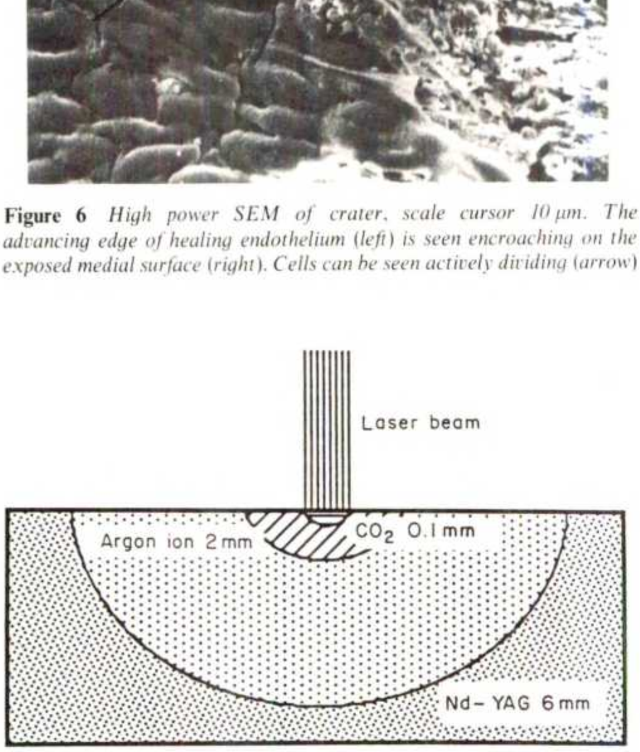

Figure 7 *The relative penetration depths into tissue of three laser wavelengths: argon ion (488 and 514·5 nm, blue-green), Nd–YAG (1064 nm, near infrared) and CO_2 (10600 nm, mid-infrared), when applied in continuous wave mode to homogeneous tissue*

across the defect and the same dying back of the medial muscle cells, though this is less marked with needle puncture. The extravasated blood also extends outwards through the adventitia in the shape of an inverted cone, though Crawford describes this as a flask-like haematoma.

The study has also measured the perforation threshold of the canine aorta to this type of laser energy under a given set of delivery conditions. These findings are unlikely to apply directly to the human aorta but they do demonstrate that tissue ablation is consistent and predictable.

It is to be hoped that little direct light will fall on normal tissue within a diseased blood vessel during laser angioplasty, and any that does will impinge upon it at an angle, thus reducing any damage. An additional safety margin is provided by fibre contact; it is not intended to fire the laser unless the fibretip is in contact with the atheroma. A further advantage of pulsed delivery is that the high peak power together with a limitation of the total energy per exposure physically prevents coagulated blood and tissue from accumulating at the fibretip; such contamination with continuous wave lasers normally leads to heating and destruction of the optical surface during contact.

Although no conclusions can be drawn from this descriptive study about the mechanism by which pulsed laser energy limits subjacent thermal damage, it suggests that pulsed Nd–YAG laser energy can be delivered safely to the peripheral circulation within the dose constraints described without fear of long-term untoward sequelae.

Acknowledgements

This work was financed by the Wright Trust (F.W.C.) and the British Heart Foundation (T.J.B.). Professor Woolf of the Bland-Sutton Institute at the Middlesex Hospital, London, UK, advised on the interpretation of the histology and Professor Charles Clark allowed us to use the facilities at the Rayne Institute. We should like to thank Adrian Kearney of the Whittington Hospital for supplying pathological material, Chrissie Moore of the London School of Hygiene for cutting the histology and Peter Rowles of the Middlesex Hospital for preparing the light and scanning electron photomicrographs.

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Paper accepted 22 December 1986

Case reports

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Diaphragmatic hernia in pregnancy

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Obstruction or strangulation of an undiagnosed diaphragmatic hernia is a rare complication of pregnancy. Previously reported cases have been associated with a high mortality particularly where early surgical intervention was not undertaken. We report an apparently unique case where a congenital diaphragmatic hernia enlarged spontaneously in labour and subsequently strangulated.

Case report

An 18 year old primigravida was admitted at 33 weeks gestation with left loin pain and vomiting. Urine microscopy revealed 40 pus cells per high power field and there was a leucocytosis of 15×10^9/l. Urinary tract infection was diagnosed. Amoxycillin and metoclopramide were prescribed and her symptoms gradually resolved. Subsequent urine culture was negative.

She was readmitted 3 weeks later with the same symptoms. In addition breath sounds were reduced over the left lung base. Proteinuria was present and recurrent urinary tract infection was diagnosed. Treatment with amoxycillin and metoclopramide was restarted. Chest radiography was not performed.

The patient's condition improved initially but spontaneous labour commenced 4 days later with subsequent fetal distress requiring caesarean section. After endotracheal intubation, reduced expansion and absent breath sounds over the left chest were noted. Endobronchial intubation was excluded. Vital signs were stable and a normal live baby boy was delivered.

Postoperative chest radiography revealed fluid levels in the left chest consistent with a diaphragmatic hernia. Conservative management with nasogastric aspiration and intravenous fluids was continued until the patient deteriorated 4 days later. Chest radiography revealed mediastinal displacement with a single fluid level in the left chest (*Figure 1*). She was transferred to the regional thoracic surgical unit.

Examination revealed tachypnoea, tachycardia, hypotension and displacement of the trachea and apex beat to the right. A chest drain was introduced via the left fifth intercostal space and 500 ml of brown fluid drained. This reduced the mediastinal compression with improvement in the patient's blood pressure and general condition.

At emergency thoracotomy the left hemithorax contained the stomach (which was distended and ischaemic but viable), the transverse colon and spleen. A tear in the stomach caused by the chest drain was closed and the viscera were returned to the peritoneal cavity. This exposed a recent 12 cm tear in the left hemidiaphragm arising from the apex of a small longstanding defect in its anterolateral costal origin. This appeared to be a congenital defect. The diaphragm was repaired with interrupted sutures. The patient made a satisfactory postoperative recovery.

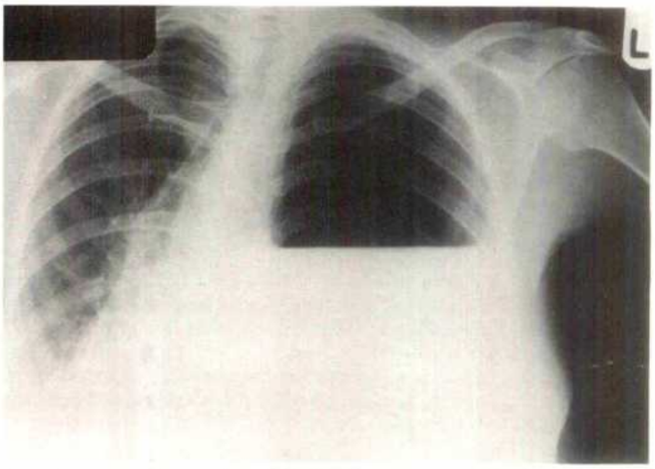

Figure 1 *Chest X-ray 4 days post partum showing single prominent air fluid level and gross mediastinal displacement*

Discussion

A hernia through the musculotendinous part of the diaphragm may be congenital (e.g. Bochdalek, Morgagni) or acquired following blunt or penetrating injury. The hernia is often asymptomatic but may obstruct or strangulate. Twenty such cases have been reported in pregnancy. Fifteen were congenital, four acquired and one spontaneous[1]. Most present in late pregnancy with abdominal pain, vomiting and dyspnoea. Diagnosis is achieved by chest radiography with contrast swallow or enema if necessary. Pleural effusion or pneumothorax may be mimicked leading to inappropriate aspiration although the patient may benefit from decompression as in the present case[2].

Conservative management is associated with a high mortality[3] and prompt surgical repair is advisable[1,4,5]. Cases presenting at term may require elective caesarean section and simultaneous or early elective repair of the hernia.

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Paper accepted 20 October 1986

0007–1323/87/050435–01$3.00

Case reports

Br. J. Surg. 1987, Vol. 74, May, 436

Spontaneous passage of a colon 'cast' in a patient with ischaemic colitis

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The first recorded case of a total cast of the left hemicolon being passed spontaneously, per anus, without the development of peritonitis, is presented.

Case report

A 64-year-old man presented with a 2 week history of sudden onset of central abdominal discomfort, watery diarrhoea and anorexia, with weight loss of approximately 3 kg. Examination revealed an unwell man, dehydrated, mildly icteric, with a low grade pyrexia and tachycardia. Abdominal examination was uncomfortable and revealed a slightly enlarged liver, a non-tender 6 cm abdominal aortic aneurysm and normal bowel sounds. On rectal examination, a firm ridge could be felt at 6 cm, suggestive of a carcinoma. Sigmoidoscopy, however, revealed a normal 6 cm rectal cuff, above which was blackened mucosa, with yellow watery fluid filling the lumen.

An electrocardiograph showed changes consistent with a recent (asymptomatic) inferior myocardial infarction. Biochemistry revealed a raised urea (19·5 mmol/l) (normal range 3·0–7·5 mmol/l) and creatinine (207 μmol/l) (normal range 53–120 μmol/l) and a moderate rise in bilirubin and liver enzymes. He had a normal haemoglobin, an ESR of 80 mm/h and a white cell count of $19{\cdot}7 \times 10^9$/l with neutrophilia (87 per cent). Stool culture did not grow any pathogens. A provisional diagnosis of ischaemic colitis was made and the patient was treated expectantly.

He remained pain free with normal bowel sounds, his diarrhoea became less frequent and his hydration quickly improved. Biochemically his renal function became normal, and his liver function tests improved.

On the seventh day after admission he suddenly and spontaneously passed 96 cm of a full thickness necrotic large bowel cast per anum.

His discomfort left him and, clinically, his condition was unchanged. He had a non-tender abdomen and normal bowel sounds. Sigmoidoscopy revealed a granulation tissue lined tract, extending up from the rectal cuff, fully of watery yellow fluid. Plain supine abdominal X-ray demonstrated a normal large bowel gas pattern up to the splenic flexure, after which there was a linear gas shadow extending down deep into the pelvis (*Figure 1*). His white cell count was $8{\cdot}4 \times 10^9$/l and histology of the bowel revealed it to be a full thickness necrotic cast of the colon. Fifteen hours later and still well having passed flatus, the patient was taken to theatre and explored through a midline incision. At laparotomy, the left colon tract was found to be completely excluded from the general peritoneal cavity by omentum and small bowel adhesions. There was a 6 cm diameter infrarenal abdominal aortic aneurysm with no pulse in the inferior mesenteric artery. The left colon's track was widely laid open and drained and the transverse colon was brought out as an end colostomy. The short rectal cuff that remained was left open to drain.

Postoperatively the patient's recovery was uncomplicated and he was discharged on the twelfth postoperative day. On the fiftieth postoperative day he had a straight Dacron graft replacement of the abdominal aortic aneurysm and remains well 8 months later.

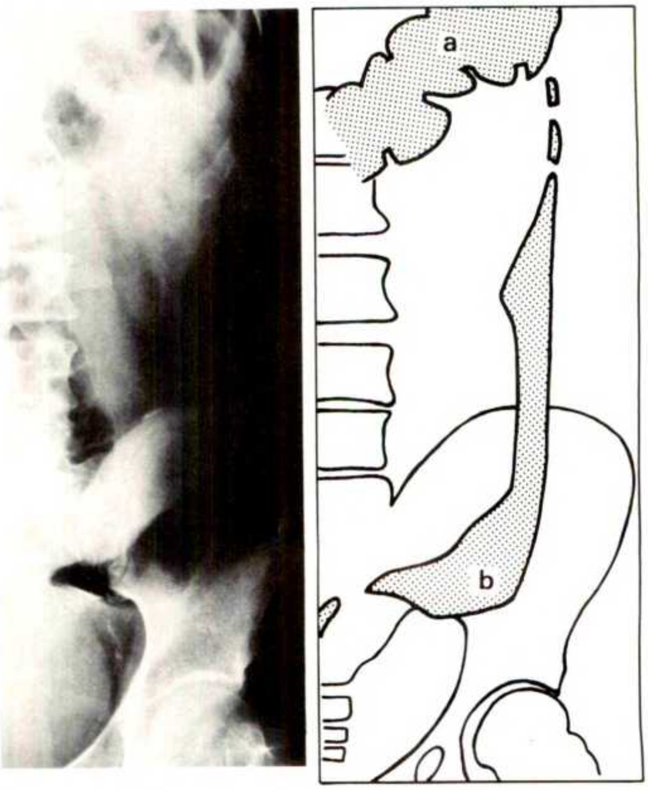

Figure 1 *X-ray after passage of necrotic large bowel cast.* **a**, *Normal colonic gas shadow;* **b**, *gas shadow in site of descending colon*

Discussion

Passage of a mucosal cast in association with ischaemic colitis has been described but only one case of passage of a full thickness colon cast has been reported[1]. That case involved a sigmoid colon cast and occurred 16 days after an emergency repair of an abdominal aortic aneurysm, a well known cause of ischaemic colitis[2,3].

This case is unusual in that the patient did not develop bloody diarrhoea and underwent transmural necrosis of the large bowel slowly, over a 2–3 week period, without the development of peritonitis or perforation. He then spontaneously passed the necrotic left hemicolon per anum. The necrotic bowel spontaneously disconnected at the edges of demarcation above and below and then without the benefit of smooth muscle peristalsis, was passed through the lumen of the viable rectal cuff and anus. The closed tube remaining was then in continuity with the gastrointestinal tract, and in fact functioned as a conduit for flatus during the next 15 h.

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Paper accepted 21 October 1986

Correspondence

Radiotherapy for benign parotid tumours

Sir

We read with interest the paper by Watkin and Hobsley (*Br J Surg* 1986; 73: 601–3).

At the Department of Radiation Oncology, Western General Hospital and Royal Infirmary, Edinburgh, patients with benign pleomorphic adenoma of the parotid were formerly treated by radium needle implant of the tumour bed following (in the majority) enucleation of the mass[1]. Of 311 patients so treated and followed for a minimum of 10 years, 14 patients developed a recurrence. In 10 patients this was histologically or clincially benign but in the other 4 malignant tumours appeared 14–18 years after therapy (1 sarcoma, 2 adenocarcinomas, and 1 carcinoma in pleomorphic adenoma). By looking at a group of 137 patients followed for 20 years, it could be determined that 2·2 per cent had developed a malignant parotid tumour.

Benign pleomorphic adenoma has a propensity to undergo spontaneous malignant transformation and this is the probable mechanism involved in three of these malignant tumours. However, the sarcoma was undoubtedly radiation-induced and radiation may well have promoted malignant transformation in the others.

Since superficial parotidectomy is as effective as local excision and radiotherapy in preventing recurrence, we agree with the authors that radiation therapy should not be used to treat this benign tumour except in special circumstances.

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Laparoscopy as an adjunct to decision making in the acute abdomen

Sir

The paper by Paterson-Brown and colleagues (*Br J Surg* 1986; 73: 1022–4) emphasizes the importance of laparoscopy to general surgeons and particularly those involved in the assessment and management of the 'acute abdomen'.

The use of laparoscopy in the way the authors suggest would have reduced their error rate to 5 per cent, but this is a somewhat hollow achievement. Five patients would have been spared an unnecessary appendicectomy, but at the expense of a general anaesthetic and a procedure not without risk. This group is the least important of those in which there was diagnostic error. Seventy-five patients (Group B (operation definitely not required) 59; Group C (wait and see) 16) were initially assessed as not requiring an operation though 6 had intraperitoneal sepsis. Laparoscopy rescued the two patients in Group C, but not the four in Group B. Therefore, laparoscopy used in the way the authors suggest would have produced a numerical improvement in accuracy by sparing five patients some inconvenience, but it could not help those whose lives were potentially at risk.

Laparoscopy undoubtedly has a role in the assessment of the 'acute abdomen', but exactly how it should be used to produce the maximum benefit for all patients remains to be established.

J. Bolton

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Authors' reply

Sir

We have read Mr Bolton's letter with interest and appreciate his points, in particular his conclusion. If laparoscopy is to make a contribution to diagnosis in the acute abdomen then an appropriate group of patients must be identified. We attempted to address this problem in our study by introducing different categories according to clinical decisions, taken as they would be if laparoscopy were not available.

We recognize the continuing truth of Mr Bolton's last paragraph but in consequence of the results obtained we have altered our protocol and, in addition to patients in group C, we now laparoscope those from group B who do not improve after 24 h of observation and women from group A (operation definitely required) with a diagnosis of 'query appendicitis'. We hope that this will allow us to come as close to eliminating inappropriate decisions in the management of the acute abdomen as is possible without laparoscoping everyone.

S. Paterson-Brown
J. R. T. Eckersley
A. J. W. Sim
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Erratum

Management of traumatic rupture of the diaphragm by C. H. Anyanwu *et al.*, *Br J Surg* 1987; **74**: 181–3. Mr C. McCollum's name was incorrectly added to the list of authors. This should have read C. H. Anyanwu, Beatrice U. O. Umeh and A. S. Swarup. We apologize to both Professor Anyanwu and Mr McCollum for this error.

Book reviews

Therapeutic Modalities in Sports Medicine

W. E. Prentice. 240 × 195 mm. Pp. 263 + xiii. Illustrated. 1986. Oxford: Blackwell Scientific. £24.00.

As an orthopaedic surgeon I have prescribed much physiotherapy. Yet physiotherapy equipment and principles remain a mystery. This book goes some way to explaining these therapeutic modalities. Dr Prentice has put together a very informative book on what is termed in America physical therapy. The mechanisms of pain are covered excellently and simply, and all the various methods of treatment including ultrasound, infra-red, and shortwave are explained in detail. The illustrations are excellent and I found the book easy to read.

I can therefore recommend this book for both physiotherapists and medical personnel.

J. P. R. Williams

Practical Guide to Free Tissue Transfer

M. H. C. Webster and D. S. Soutar. 210 × 200 mm. Pp. 125. Illustrated. 1986. London: Butterworths. £22.50.

The topic of free tissue transfer is relevant to many surgical specialties. Hence the publication of a modestly priced concise book on the subject is welcome. The size, layout and presentation of this beautifully illustrated manual immediately commend it. Its scope is catholic, ranging literally from head to foot, beginning with 'free scalp flap' and ending with 'dorsalis pedis flaps'. Continuity would be better if the upper and lower limb flaps had been described in sequence, with the sections on intra-abdominal flaps either preceding or following these.

This book is presumably intended primarily for the trainee and for the surgeon who is not a specialist in plastic surgery. For such surgeons, it would have been valuable to have described and illustrated some of the preliminary steps to the transfer techniques covered. The layout, with the text confined to the outer half of each page and the splendid line drawings on the half near the spine of the book, make this something which could easily be done by the authors in subsequent editions, which the usefulness and topicality of this little book are likely to guarantee.

P. E. Preece

A New Short Textbook of Surgery

L. Cotton and K. Lafferty. 245 × 185 mm. Pp. 362. Illustrated. 1986. Sevenoaks: Hodder and Stoughton. £12.95.

The title of this book appears misleading and unnecessary. Selwyn Taylor, the Senior Editor of a successful predecessor entitled 'A Short Textbook of Surgery', has retired and Leonard Cotton has been joined by a new editor to produce this text. A change of publishers, who include other New Short Textbooks in their series may be the reason for the change in nomenclature. Basically, it is a further edition of the previous work with a modern print, but without the sections on orthopaedics and fractures.

It is regrettable that the editors in changing the name and reducing the overall content did not attempt more radical changes in the text, and increase the number of diagrams. Some helpful clinical advice is given in the manner of handling patients, but this is sporadic and arguably better achieved in one of the many books directed to this aspect.

Opinions vary regarding the extent of material which should be presented to the undergraduate and encompass the large American tomes and the small 'Aids' series. Although somewhere between the two extremes, this book appears to be on the light side and, despite end of chapter references, the student will require further reading. Although updated, does anyone still use a mercury bougie for cardiospasm, and in a New book should 'ischaemic colitis' be regarded as 'recently described'? It would also be better editing to put the diagram of the latter in the chapter to which it refers. Even conservative modern surgeons might advise anterior resection for rectal growths below 10–12 cm and one's radiological colleagues almost universally would resist any attempt to persuade them to undertake intravenous cholangiography. Despite such criticism, the book is readable and falls within the student's price range.

D. A. Macfarlane

Postgraduate Surgery: The Candidate's Guide

M. A. R. Al-Fallouji and M. P. McBrien. 245 × 190 mm. Pp. 401 + xii. Illustrated. 1986. London: Heinemann Medical Books. £19.95.

Al-Fallouji and McBrien have produced a well researched and comprehensive guide to the final fellowship examinations. It will be particularly useful for reading shortly before the examination, being complimentary to surgical text books. There are clear sections on the written, clinical, operative and discussion parts of the examination including pathology. In some instances the degree of detail falls short of that required by many fellowship examiners but there are good, helpful and up-to-date lists for further reading. There are good sections on less commonly discussed topics such as interventional radiology, operating theatres, intensive care units, diathermy and microsurgery. The clinical radiology question and answer section is well presented and comprehensively discussed. The collection of past written examination papers should be useful and there are enjoyable historical reviews of the Royal Colleges, names to be remembered and the evolution of some important surgical procedures. Much hard work has gone into compiling this book, with facts mixed with good common sense guidance applicable to any examination. On a lighter note the St. Thomas' background of one of the authors is revealed in the advice that a candidate should 'have his hair cut and dress professionally with a three-piece dark suit, conservative tie and wear clean shoes. Smell should be acceptable.' The paucity of diagrams has helped to keep the price of the book down to £19.50. It can certainly be recommended to candidates sitting the final fellowship examinations and it may well also be enjoyed by some of the examiners.

M. H. Ashken

Minor Surgery. A Text and Atlas

J. S. Brown. 280 × 255 mm. Pp. 220 + xii. Illustrated and colour. 1986. London: Chapman and Hall. £45.00.

Recent years have seen an upsurge in enthusiasm for minor surgery amongst general practitioners, who see it primarily as a worthwhile service to provide for their patients. It has considerable attractions for the primary care consumer since it avoids hospital waiting lists, is convenient and is based in familiar surroundings. It remains, none the less, a minority activity pursued by enthusiastic altruists; the obstacle to its extension into mainstream general practice being the financial loss incurred by the GP: £5 per minor surgical procedure in 1985. This would soon change were minor surgery to attract a fee. An extension of the present range of item of service payments to include minor surgery is widely favoured by GPs and has been proposed in response to the recent green paper.

Minor Surgery: A Text and Atlas reflects this increase in interest amongst GPs. Its author, John Stuart Brown, is a general practitioner in Kent who has written extensively on the subject and this book is based on a series of articles published in *Pulse* in 1984.

It is a well produced volume, extensively illustrated and comprehensive in its scope. The practicalities of setting up, equipping and running a minor operations room in general practice are discussed in detail, followed by a description of anaesthetic methods.

A wide range of surgical procedures is described in step-by-step detail. Gynaecological, anorectal and orthopaedic procedures are covered as well as the expected 'Surgical dermatology'. The inclusion of some, such as carpal tunnel decompression and varicose vein ligation, is contentious. Few GPs would describe them as minor and their medicolegal potential is considerable. Fortunately these and anaesthetic techniques, such as the regional intravenous block suggested for the former, would not be contemplated by the vast majority, given the limited resuscitation facilities of a GP's surgery.

This volume is, nevertheless, a valuable reference book and one unlikely to gather dust on the primary care bookshelf. It will also be of value to house surgeons and doctors in accident and emergency departments, though its price tag confirms the GP as its main target!

G. P. Rubin

Diagnostic Imaging in Surgery

R. L. Eisenberg. 280 × 220 mm. Pp. 834 + xxiv. Illustrated. 1986. New York: McGraw-Hill. £135.00.

The reviewer is a general surgeon and was somewhat surprised to be asked to review a book on diagnostic imaging. This surprise changed into gratitude as the pages were turned. The foreword is by Dr Schwartz who rightly states that the dialogue between diagnostic radiology and surgery has been an ever-expanding area.

This book is compatible with *Principles of Surgery* edited by Dr Schwartz and is also closely allied to *Diagnostic Imaging in General Medicine*. The individualistic approach to diagnosis is welcomed particularly with the new appreciation of restriction of expenditure. The book is therefore of value to radiologists in planning a rational approach to diagnosis of surgical problems, and to surgeons at any stage in their career. The educational content is immense.

The Editor is the main contributor and this is revealed in a consistent approach throughout the book. Six other contributors are mentioned for particular chapters in a total of 45 chapters and 818 pages of text. The book starts with a list of chapter headings with sub-headings of a list of contents of each chapter making it very easy to use. The index at the end of the book is extensive.

The content covers every field of surgery, with the exception of otorhinolaryngology and ophthalmology. An unusual addition to the book is the presence of three valuable appendices—the first is an alphabetical list of procedures in diagnostic imaging; the second on magnetic resonance imaging and the third on intra-operative ultrasound.

Each chapter follows a similar pattern with sections on individual diseases. The section commences with a brief review of the pathogenesis followed by a description of the logical use of the appropriate investigations. The relative advantages of each of the modalities is clearly documented. Initially the reviewer was a little nonplussed by the fact that there is only occasional reference to the numerous reproductions of radiographs; isotope and CT scans and ultrasound scans. However, it soon became obvious that it is advantageous to complete the reading of the text before commencing a slightly tedious search for the appropriate figure. Each chapter has a valuable list of references, although there is a tendency to restrict these to North American literature.

Reproduction of this sort of material is always difficult in a text book, and the vast majority of the X-ray and scan reproductions are of a very high standard. All the figures have excellent descriptive sub-titles, and may have arrows indicating the main features. Not surprisingly, there is the occasional figure where the detail is less than satisfactory or the explanatory arrow is impossible to see. The scintiscans might have been clearer in colour, but this may have been difficult, and would certainly have added considerably to the cost.

The reviewer learned a great deal, not only about subjects somewhat remote from his field, but in those areas where he considered himself a reasonable expert. It is likely that another edition or another book will be necessary to review the advances in the subject which have already taken place, such as the extensive knowledge of ERCP and the developing field of intracavitary ultrasound. Nevertheless, this book clearly demonstrates the present position of the art, and puts the various modalities into a logical perspective. This book is immaculately produced in every respect, and it is easy to pick up and read any area of immediate practical relevance.

In summary this is a superb book which should be held in every hospital library, quite apart from reference libraries and should be available to all grades of staff, whether radiological or surgical. The cost is high at £135 but is money well spent.

A. A. Gunn

The Human Skeleton

R. M. H. McMinn, R. T. Hutchings and B. M. Logan. 470 × 290 mm. Illustrated. London: Wolfe Medical Publications. £15.00.

Another first rate thoroughbred from the McMinn Stables, but I feel this beautifully produced life-sized colour manual of the skeleton is a non-starter for medical students and Primary FRCS candidates.

Consisting of three life sized photographs and half a dozen other plates, it is an ideal addition to any school of nursing, sixth form college or paramedical teaching group. However, all its plates are covered, although not at this size, in previous McMinn Atlases which are so much easier to handle. This manual is double the size of the next biggest atlas and unmanageable for students, though of use for classrooms where I am sure many of these plates will spend their days being much admired.

P. Abrahams

Handbook of Surgery

S. C. Basu. 245 × 185 mm. Pp. 680 + ix. Illustrated. 1986. Calcutta, India: Current Distributors. Rs. 80.00.

The British Journal of Surgery welcomes this book on to the English language book shelves. Indian surgery is a brother of British surgery: both share the same essential ethics and techniques, both share a similar educational and assessment system but both face different challenges. Britain faces exponential health costs whilst India faces the challenge of an inexhaustible population requiring the most simple health care immediately.

Both these scenarios require trained doctors and surgeons. Both nations are addressing the problem, Britain by curtailing health care costs and academic departments, India by expanding the service and the medical schools.

This book fits the Indian problem: it consists of expanded lecture notes geared to the rapid training of many medical graduates. The book provides an excellent syntax for the surgical neophyte. It does not fit the Western requirement to train sceptical surgeons; cost, economics, evaluation and all the societal constraints of British surgery are not evident but then in India the British problems of surgery for the aged, of salvage, transplantation and to extend life do not yet command the attention of academics and government. Indian patients still welcome the cut of a sympathetic and skilful surgeon. This book is designed to teach simple surgery. I enjoyed the book which is a useful contribution to the undergraduate and junior doctor's needs in India.

H. B. Devlin

Surgical Treatment of Aortic Aneurysms

D. A. Cooley. 280 × 220 mm. Pp. 215 + iv. Illustrated. 1986. Eastbourne: Holt-Saunders Ltd. £55.00.

It is difficult to think of a surgeon more fitted to write on this topic. Dr Cooley in association with his Houston colleagues was involved in many of the earliest operations in which aneurysms of the aorta were successfully resected and replaced by synthetic grafts. As Dr Griepp points out in the foreword, Dr Cooley and Dr DeBakey reported the first successful resection of an aneurysm of the thoracic aorta in 1954 and of the distal aortic arch later the same year. In 1955 they reported the first total excision of an aneurysm of the aortic arch and by 1958 they had reported a series of 179 thoracic aortic aneurysms treated by resection. This book deals with aneurysms at every level of the aorta. The introduction covers the history of aneurysm surgery and the development of prosthetic materials. Several techniques for combining aortic valve replacement with replacement of various portions of the ascending aorta, the arch and their various branches are well covered. Acute and chronic dissections of the aorta are described at length. The principal concern in the replacement of aneurysms of the descending thoracic aorta is ischaemic injury to the spinal cord. It was interesting to see that Dr Cooley has abandoned the methods described for preventing ischaemia such as using various forms of bypass. He now simply uses aortic cross-clamping without any supportive measures, relying on the expeditious removal of the aneurysm and restoration of pulsatile flow, making the observation that periods of 30 min of total occlusion are well tolerated with a low incidence of paraplegia. This implies fast and skilful surgery—qualities for which Dr Cooley is well known. Techniques of replacement of thoraco-abdominal aneurysms have been simplified in similar fashion with the use of rapid inlay techniques. When we come to the description of techniques for replacement of the infrarenal aorta most vascular surgeons will be on very familiar ground but even here many useful points emerge. For example a number of alternative techniques for dealing with horseshoe kidney are shown, as are methods of dealing with graft infection and aortoduodenal fistula. Aneurysmal disease and obliterative disease commonly co-exist and a lengthy chapter deals with techniques for disobliterating or reconstructing aortic branches from the coeliac to the femorals. Graft complications are included.

The final section reviews the results of 2465 aortic aneurysm patients—a phenomenal series. This like the rest of the book makes fascinating reading. The text is notable for its clarity and relevance. There is an extensive bibliography. The illustrations, mainly line drawings, are excellent. For a monograph of this size this book is expensive but I suspect most vascular surgeons will find it difficult to resist.

C. V. Ruckley

Notices and announcements

Meetings

20–23 May 1987
78th Annual Meeting of the American Association for Cancer Research
Atlanta, Georgia, USA
Information: Margaret Foti, American Association for Cancer Research Inc., Temple University School of Medicine, West Building, Room 301, Broad and Tioga Streets, Philadelphia, PA 19140, USA

22 May 1987
British Association of Endocrine Surgeons
Edinburgh, UK
Information: Mr A. W. Goode, Honorary Secretary to the British Association of Endocrine Surgeons, Surgical Unit, The London Hospital, Whitechapel, London E1 1BB, UK

24–30 May 1987
Annual General and Scientific Meeting of the Oto-laryngological Society of Australia
Surfers Paradise, Queensland, Australia
Information: OLSA Meeting Secretariat, PO Box 731, Toowong Q4066, Australia

25–28 May 1987
European Society for Therapeutic Radiology and Oncology Sixth Annual Meeting
Lisbon, Portugal
Information: Professor Dr E. van der Schueren, Department of Radiotherapy, Kapucijnenvoer 35, 3000 Leuven, Belgium

1–3 June 1987
International Congress of Abdominal Infections
Hamburg, FRG
Information: D. H. Wittmann, Priv. Doz. Dr. I. Chir. A K Altona, Paul-Erlich-Strasse 1 D-2000, Hamburg 50, FRG

6–7 June 1987
Course on the Applied Surgical Anatomy and Operative Surgey of the Liver, American Association of Clinical Anatomists
Toronto, Canada
Information: Dr R. Ger, Winthrop University Hospital, Mineola, NY 11501, USA

10–12 June 1987
69th Meeting of the Endocrine Society
Indianapolis, Indiana, USA
Information: The Endocrine Society, Annual Meeting Office, 428 E Preston Street, Baltimore, MD 21202, USA

10–13 June 1987
Third International Conference on Malignant Lymphoma Current Status and Prospects
Lugano, Switzerland
Information: Dr F. Cavalli, Head Division of Oncology, Ospedale San Giovanni, CH-6500 Bellinzona, Switzerland

15–19 June 1987
Advanced Hepato-Pancreatico-Biliary Surgery
Lund, Sweden
Information: Professor S. Bengmark, Box 5121, S-220 05 Lund 5, Sweden

22–26 June 1987
Peritoneum and Peritoneal Access
Lund, Sweden
Information: Professor S. Bengmark, Professor of Surgery, Box 5121, S-220 05 Lund 5, Sweden

24–28 June 1987
Annual Meeting of the Western Thoracic Surgical Association
Colorado Springs, USA
Information: Western Thoracic Surgical Association, 13 Elm Street, Manchester, MA 01944, USA

7–8 July 1987
Blood Flow '87 (Biological Engineering Society – Blood Flow Group)
University of Leeds, UK
Information: Mr R. Price, Department of Medical Physics, Leeds General Infirmary, Leeds LS1 3EX, UK

9–10 July 1987
Surgical Research Society Meeting
Leeds, UK
Information: Professor I. Taylor, Surgical Research Society, University Surgical Unit, F Level, Centre Block, Southampton General Hospital, Tremona Road, Southampton, UK

9–11 July 1987
XIIth International Update on Liver Disease
London, UK
Information: Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

11–12 July 1987
Summer 1987 Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, c/o Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

31 August–4 September 1987
Surgical Efficiency and Economy
Lund, Sweden
Information: Professor S. Bengmark-SEE, Box 5121, S-220 05 Lund 5, Sweden

9–11 September 1987
Clinical Controversies in Inflammatory Bowel Diseases
Bologna, Italy
Information: Organizing Secretariat, SO.GE.PA.CO. Spa. piazza Constituzione, 5/c, 40128, Bologna, Italy

15–18 September 1987
The British Society of Gastroenterology Jubilee Meeting
London, UK
Information: The Administrative Secretary, The British Society of Gastroenterology, 3 St Andrew's Place, Regent's Park, London NW1 4LB, UK

18–22 September 1987
69th Annual Meeting of the American Association of Oral and Maxillofacial Surgeons
San Francisco, California, USA
Information: K. H. Hajduk, 211 East Chicago Avenue, Suite 930, Chicago, Illinois 60611, USA

9–14 October 1988
The Australian Cranio-Maxillo-Facial Foundation International Workshop on Cranio-Facial Trauma
Adelaide, South Australia
Information: Mrs D. Moody, Executive Officer, 226 Melbourne Street, North Adelaide S A 5006, Australia

11–16 October 1987
Annual Clinical Congress of the American College of Surgeons
San Francisco, California, USA
Information: American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

15–17 October 1987
Fourth Meeting of the European Chapter of the International Union of Angiology
Brussels, Belgium
Information: Madame D. Shanni, Administrative Secretariat, ECCO, Rue Vilain XIIII, 17a, B-1050 Brussels, Belgium

18–24 October 1987
Recent Advances in Pancreaticobiliary Surgery
Glasgow, UK
Information: Professor D. C. Carter, University Department of Surgery, Queen Elizabeth Building, Royal Infirmary, Glasgow G31 2ER, UK

22–23 October 1987
First British Symposium on Surgical Stapling
Manchester, UK
Information: Conference Coordinates, Confer House, 69 Kingston Road, New Malden, Surrey KT3 3PB

Leading article

Br. J. Surg. 1987, Vol. 74, June, 441–442

Carcinoma of the exocrine pancreas: a sex hormone responsive tumour?

Pancreatic carcinoma remains a disease that is difficult to diagnose and unsatisfactory to treat. Most patients who develop the disease die within 6 months of diagnosis, and over 90 per cent are dead within one year. A possible new approach to treatment was suggested in 1981 when the presence of high concentrations of oestrogen receptors, in both the cytoplasm and nucleus, was demonstrated for the first time in human pancreatic adenocarcinoma of ductular origin[1]. This work has been confirmed by other groups both in human tumours and in experimentally induced tumours in rats[2,3]. Evidence that these receptors were important came with the finding of progesterone receptors within tumour tissue[4]; these require the presence of functioning oestrogen receptors for their formation[5]. More recently androgen receptors have been demonstrated using improved sensitivity techniques[6], refuting earlier work when these receptors could not be found[7]. All three sex steroid receptors have now been demonstrated in pancreatic carcinoma tissue.

Enzymes which are distributed in conventional oestrogen and androgen target tissues such as uterus, prostate and breast cancer have now been demonstrated in pancreatic carcinoma[8]; aromatase converts testosterone to oestradiol, and 5α-reductase converts testosterone to its more active metabolite 5α-dihydrotestosterone. Both of these enzymes require testosterone as their substrate, so it was speculated that uptake by the tumour would lead to lower serum concentrations.

This hypothesis was given firm support when levels well below the normal range were demonstrated in all male patients, and low normal levels were found in all female patients[9]. This work has also been confirmed by other groups[10–12]. However, serum testosterone levels are not useful in diagnosis as some patients with other malignant diseases may also have low circulatory levels. These studies strongly suggest that pancreatic cancer should now be considered with carcinoma of the breast and prostate as a hormone responsive neoplasm, and that hormone manipulation may offer a new approach to the treatment of pancreatic carcinoma.

Confirmatory evidence that these studies may have therapeutic implications for patients came when two groups demonstrated the inhibiting effect of hormone manipulation on the growth of human pancreatic adenocarcinoma xenografts in nude mice, and the growth potentiating action of testosterone on both xenografts and cells in tissue culture[13,14]

Human studies are now urgently required. To date, two phase II studies using tamoxifen (Nolvadex) in patients with unresectable pancreatic carcinoma have demonstrated an increase in median survival, and an increased number of patients with long survival. Four of ten patients lived more than 14 months in the Danish study[15], and three of fourteen lived to 22 months in the Swedish report[16]. There has also been an encouraging preliminary report of the use of an analogue of luteinizing hormone-releasing hormone (LHRH) in five patients[17], significant benefit having been obtained earlier in animal models of pancreatic carcinoma[18]. LHRH lowers serum testosterone levels and has been used successfully in prostatic carcinoma. One of the five patients with pancreatic cancer had a Stage IV tumour[19] with liver metastases and lived for 16 months, having previously had a re-look laparotomy at 11 months when reduced tumour bulk was noted. All five patients showed clinical and subjective improvement. This small study provided further support for the apparent central role of testosterone in tumour growth as had been demonstrated in the earlier experimental work.

Anecdotal reports of small uncontrolled, unpublished studies using tamoxifen have not shown any therapeutic success. However, the phase II studies reported to date lend strong support to the therapeutic role for hormonal manipulation in the treatment of pancreatic carcinoma. Certainly, alteration of the hormonal milieu is not a cure for this tumour, just as it is not for either breast or prostatic carcinoma, but it may be a major advance in the treatment of what is virtually an untreatable malignancy.

At present a number of phase III trials of hormonal therapy in pancreatic carcinoma are in progress. Three large studies include (i) a double blind trial of tamoxifen *versus* placebo in Norway which will contain over 150 patients for analysis in mid 1987; (ii) tamoxifen *versus* an untreated control group in Stockholm, Sweden and

0007-1323/87/060441-2$3.00

(iii) estramustine (Estracyt), a combined oestrogen–mustine compound, *versus* a control group in Lund, Sweden. A multicentre trial, centred on the Liver Unit, King's College Hospital, of tamoxifen *versus* cyproterone acetate (an anti-androgen) *versus* an untreated control group has just been completed. The cyproterone treated group showed no difference in survival when compared with the control group, 4 of 32 patients surviving to 1 year, whereas 8 of 37 patients treated with tamoxifen survived more than 1 year. Four of these patients are still alive at over 20 months (unpublished observations by kind permission of Dr Roger Williams. A British double blind study comparing tamoxifen to a placebo is being started soon based at Leeds and 70 patients will be recruited to each group.

Other hormonal therapies should now be investigated in phase II trials. All agents shown to have been effective in either breast or prostatic carcinoma are worthy of study. Possibilities include progestogens, anti-androgens, orchidectomy (which has firm support from animal studies[20]), aminoglutethimide (which offers medical adrenalectomy as well as aromatase inhibition), and 'debulking' operations with hormone therapy especially in Stage I and II disease. Perhaps the time will come when a relay of hormonal treatments should be used as in breast cancer; as one fails another is used. It is now just possible that the clinician may have a little more to offer the patient with pancreatic carcinoma than just the relief of jaundice, symptomatic and supportive therapy, and a feeling of utter hopelessness projected from the end of the bed.

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Br. J. Surg. 1987, Vol. 74, June, 443–448

Reflux stricture of the oesophagus

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Benign oesophageal stricture remains a common problem. Following accurate diagnosis, early treatment allows dilatation in the great majority of patients. Resection can frequently be avoided and in fit patients dilatation should be combined with an anti-reflux operation plus gastroplasty where necessary. Frail elderly patients may be managed by continued dilatation and medical means to reduce and combat the effects of reflux. Resection should now be necessary in only about 5 per cent of patients and colonic interposition offers good long-term results. It must be remembered that adenocarcinoma is a small but real risk in patients with reflux stricture

Keywords: Gastro-oesophageal reflux, stricture, anti-reflux surgery

There are many causes of benign oesophageal stricture (*Table 1*) of which the most common is severe oesophagitis and this review is confined to those strictures complicating gastro-oesophageal reflux disease. Despite advances in our understanding of the pathophysiology of gastro-oesophageal reflux and more sophisticated means of investigation, reflux stricture remains a relatively common and challenging clinical problem. The last decade has seen a considerable change in emphasis in the management of reflux stricture, with perhaps less uniformity as patients may come under the care of specialist oesophageal surgeons, general surgeons, thoracic surgeons or gastroenterologists. This review describes current concepts in the pathophysiology and diagnosis of reflux stricture and discusses the current status of the various treatment methods.

Pathophysiology

The oesophageal mucosa is extremely sensitive to damage by acid or alkali, initially resulting in oesophagitis with cellular infiltration, oedema, basal cell hyperplasia, increasing depth of the vascular papillae and a varying degree of fibrosis[1,2]. As the oesophagitis progresses, erosions occur which subsequently become confluent and extend proximally, initially as tongue-like projections but later progressing to circumferential areas of damage. If such lesions heal, they do so by replacement with columnar epithelium which grows upwards from the cardia, resulting in an altered configuration of the Z line and, ultimately, in its proximal migration to form Barrett's oesophagus.

Continued reflux in these circumstances leads to progressive tissue damage and fibrosis, commencing initially at the squamocolumnar junction, wherever that may lie, but in severe cases extending proximally over a variable length. In the early stages, strictures are often soft, associated principally with spasm, oedema and the laying down of immature collagen which is usually confined to the submucosa (grade 1). Maturation of the collagen and further fibrosis results in a hard, annular stricture, the pathological changes still being confined to the submucosa (grade 2). More severe cases are associated with mucosal ulceration, the inflammatory and fibrotic process becoming transmural with muscular involvement and frequently perioesophagitis which extends longitudinally, resulting in oesophageal shortening (grade 3).

Stricture formation is almost invariably associated with severe degrees of reflux or reflux of long duration, but depends on a balance existing between aggressiveness of the refluxate and oesophageal mucosal resistance and efficiency of clearance. Patients with strictures often have the lowest values of resting lower oesophageal sphincter (LOS) pressure and reflux predominantly in the supine position[3]. They frequently have motility disturbances which are exacerbated by transmural stricture formation[4]; extreme examples are the relatively early stricture formation which occurs in the reflux associated with scleroderma and systemic sclerosis, and following treated achalasia. Some evidence exists to suggest that alkaline reflux is more likely to produce more severe degrees of oesophagitis and stricture formation than reflux of acid/pepsin[5,6]. Antro-duodenal dysmotility as well as organic gastric outlet obstruction may increase the potential for reflux.

Diagnosis

The patient invariably presents with dysphagia and this is frequently the first indication of reflux disease. In 120 cases previously reported[7], 68 per cent did not have an antecedent

Table 1 *Principal causes of benign oesophageal stricture*

Congenital
  Oesophageal atresia
  Webs
  Tracheobronchial remnants
Infection
  Moniliasis
  Tuberculosis
  Crohn's disease
  Typhoid
Injury
  Caustic burns
  Irradiation
  Nasogastric intubation
  Endoscopic injury
Postoperative
  Anastomosis
  Closure of perforation
  Diverticulectomy
Medication
  Tetracycline
  Aspirin
  Non-steroidal anti-inflammatory drugs
  Progesterone-containing contraceptive pills
  Theophylline and derivatives
  Certain anticholinergic drugs
Reflux oesophagitis and complications

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diagnosis of gastro-oesophageal reflux, although a suggestive history could be elicited in 76 per cent. A careful history is essential to exclude caustic or drug ingestion, and eliminate more obvious predisposing factors such as previous surgery, radiotherapy, endoscopy or nasogastric intubation.

A barium swallow is useful to exclude other structural causes of dysphagia (such as pharyngeal pouch, webs or obvious neoplasm) and to assess the site and length of the stricture. This complements the information obtained at oesophagoscopy, especially where the stricture is impassable. Oesophagoscopy allows mucosal visualization and histological confirmation of the diagnosis. Our preference is to use fibreoptic endoscopy, and the combination of punch biopsies and brush cytology increases diagnostic accuracy to over 90 per cent[8]. In grade 1 and some grade 2 strictures, gentle passage of the fibreoptic paediatric endoscope will allow inspection of the lumen of the stricture and the distal oesophagus and stomach. In more advanced strictures, this can often be accomplished after gentle dilatation (see below).

The demonstration of gastro-oesophageal reflux is essential to the diagnosis and correct management of reflux stricture. Reflux may often be suggested on barium swallow or oesophagoscopy, but manometry and pH recording are necessary to quantify the reflux, categorize its type, and identify coexisting motility problems, all of which may have important therapeutic implications. Manometry and pH recording are facilitated by prior dilatation of the stricture, especially if dual probe simultaneous monitoring of gastric and oesophageal pH is to be undertaken to assess the contribution of alkaline reflux.

Some of the more severe degrees of acid or alkaline reflux are seen in patients with stricture. These patients often reflux predominantly in the supine position, and such patients have a 25 per cent incidence of reflux stricture[3]. Motility studies show an increased incidence of disordered motor activity, with low amplitude contractions in the distal oesophagus, these changes being progressively more marked as panmural inflammation and scarring progress[9]. A vicious circle is established if the lower oesophageal sphincter is involved in the process, with progressive decrease in tone allowing more reflux. As certain motor disorders, notably scleroderma, predispose to more severe oesophagitis and stricture formation, characteristic changes of total ablation of the LOS and gross diminution or loss of peristaltic activity may be found. A similar loss of peristaltic activity is seen in achalasia complicated by gastro-oesophageal reflux after forcible dilatation or myotomy. Organic stricture formation is common because of impaired oesophageal clearing capacity in these circumstances, but LOS tone may be present although relaxation remains impaired. It is clearly of vital importance to perform careful manometric studies where anti-reflux surgery is contemplated, to ensure that peristalsis is adequate and that LOS relaxation occurs. Otherwise severe obstructive problems may be an undesirable consequence of treatment.

Philosophy of management

The development of reflux stricture is a serious consequence of severe and prolonged oesophageal exposure to acid or alkaline refluxate, and demands active treatment. Stricture development during conservative management of gastro-oesophageal reflux represents failure of such treatment. In general, the aims of therapy are to improve swallowing and prevent further oesophageal damage as effectively and safely as possible. While a surgical approach is most likely to fulfil the former criterion, the age and general condition of many patients with reflux stricture often precludes an aggressive approach. Of 120 patients with reflux stricture previously reported from our unit[7] the mean age was 69·5 years and the oldest patient was 92. In practical terms, a balance has to be struck between the age and condition of the patient and the severity of the stricture when selecting the form of treatment most appropriate to the individual circumstances, acknowledging the fact that many grade 1 and some grade 2 strictures respond to less active forms of management. Management methods can be categorized as non-operative or operative.

Non-operative management

Non-operative management may be considered initially in grade 1 and some grade 2 strictures and in all cases where the patient's age or general condition precludes more active intervention. The essential components of non-operative treatment are:

(1) dilatation of the stricture
(2) control of reflux
(3) surveillance.

Dilatation of reflux stricture

Dilatation of oesophageal strictures has taken numerous forms since the first report of its use in 1922[10] (*Table 2*). Most of the early techniques involved the unguided passage of dilators through a rigid oesophagoscope. However, guided techniques using the fibreoptic endoscope have gained popularity since their introduction in 1971[11], largely because of the avoidance of general anaesthesia and the lower risk of perforation[12]. All the techniques, with the exception of the Didcott dilator[13], apply a tangential force from above, but the recent application of polyvinyl balloons is a more logical attempt to apply a coaxial force to stricture dilatation[14]. Microvasive balloons which pass through the biopsy channel of a fibreoptic endoscope are currently being evaluated.

Since 1975, we have treated 168 patients with benign oesophageal strictures. In patients treated by dilatation, our early practice of unguided dilatation with gum-elastic bougies through the rigid oesophagoscope was superseded in 1977 by guided dilatation using fibreoptic endoscopy. During the first 3 years of fibreoptic endoscopic dilatation, we used the Eder–Puestow system as described by Lilly and McCaffrey[11], but since 1980 we have used Celestin bougies[15]. These cause less pharyngeal trauma because they are made of soft thermoplastic PVC as opposed to metal and because progressively graded increase in diameter allows dilatation from 12 FG to 56 FG with only two insertions. Savary dilators are similarly less traumatic, although a separate dilator is used for each increment in size, making multiple passages necessary.

The principal advantages of fibreoptic endoscopic dilatation are that it can be performed without general anaesthesia as an outpatient procedure, sedation with diazepam and pentazocine is usually adequate, and the risk of perforation is low. We have performed over 500 such dilatations since 1976 without mortality, the only morbidity being two perforations which were successfully treated[16]. Such ease of performance lends itself to an efficient 'open-access' system for repeated dilatations of known patients, who in our hospital telephone the endoscopy unit when their swallowing deteriorates and a further dilatation is then arranged.

Table 2 *Types of dilator used in management of benign strictures*

Unguided systems
  Gum-elastic bougies
  Chevalier–Jackson dilators
  Maloney and Hurst mercury-filled bougies
Guided systems
  String-guided dilators
  Wire-guided: Eder–Puestow
    Celestin
    Savary
Continuous coaxial systems
  Didcott dilator
  Lunderquist balloon
  Microvasive balloon

Table 3 *Results of randomized controlled trial comparing the effect of medical and surgical reflux control on dilatation requirements in reflux stricture*[22]

	Medically treated group (Gaviscon 40 ml + cimetidine 800 mg/day) ($n = 16$)	Surgically treated group ($n = 16$)
Percentage requiring single dilatation only	44	75
Mean number of dilatations over mean follow-up period of 22 months	1·8	0·3

Data on the efficacy of dilatation are rather sparse, and mostly relate to fibreoptic endoscopic dilatation. Benedict[17] reported a success rate of 70 per cent, Lanza and Graham[18] one of 79 per cent and Wesdorp and Tytgat one of 88 per cent[19]. Success in the context of these reports refers to the avoidance of surgical intervention, and the progressive increase in success rates in these series was attributed to the progressive increase in diameter to which strictures were dilated routinely. However, the avoidance of surgery does not equate with success except in the eyes of the most conservative physician, and a uniform policy of dilating to a predetermined size in all circumstances may be inappropriate in view of the variation in types of stricture and the stage at which they first present. Other criteria used to assess efficacy have been the effect on stricture diameter as measured by barium studies and the passage of radio-opaque spheres[20], and the number of dilatations over a finite follow-up period[7,21].

In the study of Ogilvie *et al.*[22], 40 per cent of patients treated by dilatation and pharmacological anti-reflux preparations did not need further dilatation, the frequency of dilatation decreasing with time to a mean of 0·6 dilatations per patient per year 3 years after the initial dilatation, although some individuals required up to 18 dilatations over a 4-year period. In 78 patients treated in our unit by a similar regimen, 41 per cent needed only one dilatation while the remainder required a mean of 3·1 further dilatations in a mean follow-up period of 3·3 years. In 42 patients in whom control of reflux was achieved surgically, 71 per cent needed a single dilatation only; the mean number of dilatations required in the remainder over the same follow-up period was 1·6.

Of the various guided dilatation systems available, the Eder–Puestow system has been compared with the Celestin[23] and the latter with the Lunderquist balloon[24]. There was no apparent difference in efficacy between the various systems, but the Celestin system is less traumatic than the Eder–Puestow and considerably less expensive than the PVC balloons which have a limited life. The most popular of the non-guided forms of dilatation is the use of Maloney tapered mercury bougies, which lends itself to outpatient management of strictures without the need for endoscopy and is therefore useful in frail, elderly patients. Bremner[25] reported good results in selected, poor risk patients, with approximately half requiring only a single dilatation. The principal disadvantage is the lack of surveillance if endoscopy is avoided, but this is of limited practical importance in the poor risk patients in whom the technique is most appropriately used.

Control of reflux

A detailed discussion of the non-operative treatment of gastro-oesophageal reflux is outside the scope of this review, but suffice it to say that in those patients with reflux stricture in whom surgery is inappropriate, it is illogical to perform intermittent dilatation without attempting pharmacological reflux control. Agents employed should be appropriate to the nature of the refluxate, the pattern of oesophageal exposure and the clearing capacity of the distal oesophagus.

The superiority of surgical over medical control of reflux is, however, particularly reflected in the management of reflux stricture. Not only have strictures been shown to resolve with effective anti-reflux surgery alone (see below), but a controlled trial conducted in our unit showed a significantly reduced need for subsequent dilatation in the group treated by surgery in conjunction with dilatation. The need for dilatation in these patients was reduced to approximately half of that in the medically treated group (*Table 3*).

Surveillance and the cancer risk

Many series of reflux stricture report an incidence of 2·5–4 per cent for the development of adenocarcinoma[7,21,26]. This is hardly surprising, since up to 76 per cent of some series of reflux stricture comprise patients with columnar-lined (Barrett's) oesophagus[27,28], in which condition there is abundant evidence of malignant potential[29–31]. We have seen oesophageal adenocarcinoma develop in four patients undergoing intermittent dilatation and pharmacological anti-reflux therapy, 18–30 months after initial diagnosis at which time both punch biopsies and brush cytology were negative[7]. Knowing the natural history of untreated oesophageal adenocarcinoma, it seems inconceivable that these lesions could have been present from the outset.

These observations suggest the need for regular surveillance of patients on an intermittent dilatation programme, especially those with columnar-lined oesophagus, although there is clearly less need in frail, elderly patients unfit for active treatment of an adenocarcinoma if this were to develop. Regular endoscopy and cytology is desirable at least annually and it is our practice to perform these at each dilatation, taking particular care in patients with increasing dilatation requirements. When adenocarcinoma supervenes, it should be treated according to normal practice, although because of the age and general condition of many patients suffering from reflux stricture, palliative management may be all that is appropriate. Two of our patients developing oesophageal adenocarcinoma were suitable for resection, the other two elderly patients being treated by fibreoptic endoscopic intubation. The question of dysplasia is less easy, demanding at the very least careful regular surveillance with repeated biopsy and cytology, some workers advocating prophylactic resection where dysplasia is severe[32].

Operative management

The last two decades have seen a swing away from resection to a more conservative approach in the majority of cases, based on dilatation of the stricture and correction of reflux. The disadvantage of resection is the operative mortality of up to 15 per cent[33] and the fact that the potential for reflux may remain. The relative safety and efficacy of dilatation combined with anti-reflux surgery now allows a more radical approach than intermittent dilatation alone. The approach allows suitable patients to be treated earlier in the course of the disease, such that resection is now rarely necessary in benign reflux stricture. The range of surgical approaches currently used in the management of reflux stricture will each be considered.

Anti-reflux surgery alone

The beneficial effect of anti-reflux surgery alone in the healing of strictures was suggested by Burkhart and Sullivan in 1972[34], with improvement in 12 of the 17 patients treated. This finding was subsequently confirmed by Larrain *et al.*[35] who added some objectivity by measuring stricture diameter before and after Hill posterior gastropexy without dilatation. Mean stricture diameter increased from 6·3 mm pre-operatively to 13·0 mm postoperatively in 24 patients who were felt to have true fibrous stricture using endoscopic and manometric criteria.

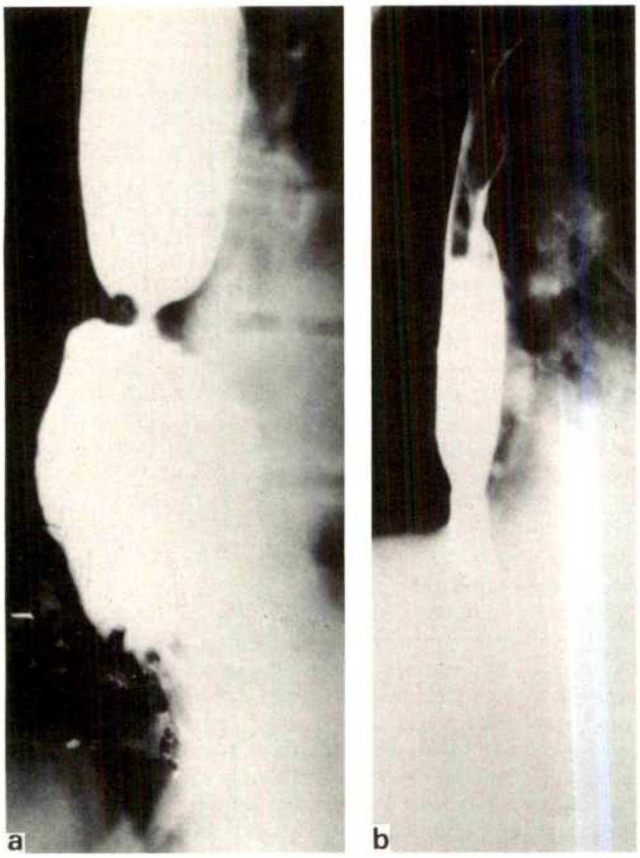

Figure 1 *Barium swallow of patient with fibrous reflux stricture before* (**a**) *and after* (**b**) *anti-reflux surgery without dilatation*

While it is our practice to combine dilatation with anti-reflux surgery, we have confirmed the resolution of strictures in four patients treated by anti-reflux surgery alone, each of whom had a true fibrous stricture impassable with an Olympus GIFP3 9 mm endoscope (*Figure 1*).

Anti-reflux surgery combined with dilatation

In a situation where correction of reflux alone heals some strictures, and where 75 per cent of patients having anti-reflux surgery and dilatation do not require subsequent dilatations, the combination of anti-reflux surgery and dilatation is currently the preferred form of management. The patient must be fit to undergo surgery and should not have an advanced grade 3 stricture, such that perioesophagitis and shortening preclude an adequate anti-reflux operation.

Dilatation may be performed either immediately before surgery by one of the techniques previously described or intra-operatively through a gastrotomy. Most of the current anti-reflux operations have been performed in this context. Bremner[25] reported good results using the Nissen fundoplication in 25 patients, but Ellis *et al.*[36] were less enthusiastic reporting a high incidence of residual dysphagia and need for further dilatations, and suggested that total fundoplication may be inappropriate in patients with stricture. Skinner[37] reported good results with the Belsey Mark IV operation after a previous, less encouraging report. Consistently good results have been reported with the Hill gastropexy[38,39], Hemrick and Coates[39] reporting a success rate of 96 per cent. However, the overall results of a large review of 17 pooled series including each of the above-mentioned procedures reported a mean success rate of approximately 75 per cent[28].

The rather lower success rate than that usually achieved in uncomplicated reflux disease is due to a combination of greater difficulty in achieving complete reflux control, especially in the presence of oesophageal shortening, and the fact that the accompanying motility problem produces the potential for oesophageal obstruction after total fundoplication. This latter problem is most marked in patients with underlying primary motility disorders, in whom the success rate is as low as 58 per cent[3].

Our preferred anti-reflux procedure is one which depends on transhiatal mobilization and fixation of a long intra-abdominal segment of oesophagus to a posterior crural repair, thus placing the majority of the LOS under the influence of positive intra-abdominal pressure. It also depends on accentuation of the flutter valve at the cardia. These factors result in the need for only a 120° fundoplication to achieve reflux control, as demonstrated objectively by 24 h pH recording[40]. We have performed this procedure in 248 patients with gastro-oesophageal reflux over an 11-year period, including 68 patients with reflux stricture. There has been no mortality and minimal morbidity; in particular there has been no gas bloat, no necessity to re-operate for mechanical complications and no obstructive symptoms other than transient dysphagia in approximately 6 per cent of patients which almost invariably resolved spontaneously prior to discharge from hospital.

Subjective results have shown improvement in 97 per cent of patients with objective evidence of reflux control on 24 h pH monitoring in 85 per cent. Manometric studies have shown that the range of resting LOS pressure is similar to that of our asymptomatic controls[41], as distinct from the Nissen fundoplication which in several reports results in supraphysiological values of resting LOS pressure[42,43]. It is likely that this has bearing on the incidence of obstructive complications, particularly when motor abnormalities coexist with reflux and may explain the problems encountered with the Nissen fundoplication by Ellis *et al.*[36]. In common with other workers, our proportion of good results in stricture patients is somewhat smaller than that obtained in uncomplicated reflux patients but, at 81 per cent, compares favourably with other series (*Figure 2*).

In situations where extensive perioesophagitis and oesophageal shortening preclude the easy conduct of a

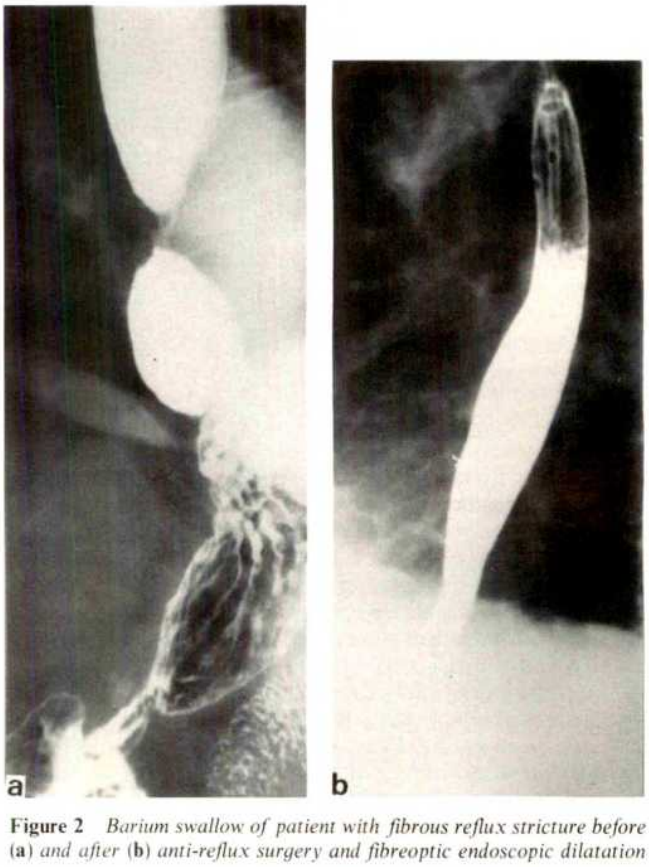

Figure 2 *Barium swallow of patient with fibrous reflux stricture before* (**a**) *and after* (**b**) *anti-reflux surgery and fibreoptic endoscopic dilatation*

transabdominal anti-reflux procedure, a transthoracic or thoraco-abdominal approach allows greater mobilization of the oesophagus. Indeed, a Nissen fundoplication situated within the chest has been shown to control reflux effectively[44] although a disturbing incidence of gastric ulceration and even perforation has been reported[45]. Current opinion now favours the combination of a gastroplasty to gain length, together with an anti-reflux operation when there is any doubt about the ability to perform a safe, effective anti-reflux procedure in the presence of oesophageal shortening.

Gastroplasty with anti-reflux surgery and dilatation

The most popular gastroplasty is that described by Collis[46], which creates a 5 cm length of intra-abdominal 'oesophagus' from a gastric tube. This aids reflux control by providing a pressure gradient between the segment exposed to positive intra-abdominal pressure and the intrathoracic oesophagus under the influence of negative intrathoracic pressure. It also provides a structure around which a varying degree of fundoplication may be performed, most popularly a Belsey or Nissen repair, and we have combined gastroplasty with the repair described above with good effect.

Pearson[47] has reported the largest series of the Collis/Belsey procedure, 166 of his 360 procedures being performed for reflux stricture. Satisfactory results were obtained in 85 per cent of patients, with equally good results in patients with stricture, although subsequent resection was necessary in two such patients. Orringer[48] and Ellis[36] have both reported superior results in their hands with the Collis/Nissen procedure when reflux control has been measured objectively. In Orringer's series, 93 per cent achieved good reflux control, but of 30 patients so treated, half required subsequent dilatations and 2 needed regular dilatations because of unsatisfactory resolution of their strictures.

Since around 95 per cent of reflux strictures are dilatable and can regress with adequate reflux control[49], the trend towards dilatation with anti-reflux surgery, with or without gastroplasty, has resulted in a marked movement away from resection over the last two decades. This has resulted in considerable lowering of operative mortality, from around 15 per cent to nearer 1 per cent, and in better control of reflux. In view of the risk of adenocarcinoma complicating reflux stricture and the fact that anti-reflux surgery may not result in regression of columnar-lined oesophagus[36], the carcinoma risk might be expected to persist when resection is not performed. All the cases of adenocarcinoma complicating peptic stricture in our unit[7] occurred in medically treated patients; no patient who has undergone anti-reflux surgery has subsequently developed carcinoma. However, Pearson[47] reported three adenocarcinomas in 166 patients treated by the Collis/Belsey procedure and dilatation, and has suggested the need for regular surveillance of these patients. Skinner *et al.*[32] have even advocated resection in those cases with severe dysplasia.

Resection and interposition

For the reasons just outlined, the overall incidence of resection has fallen to 5 per cent or less, only three resections for reflux stricture having been performed in our unit in the past decade. Resection should be reserved for patients resistant to the more conservative technique, and these are often individuals who have associated motor disorders or who have undergone multiple operations. Several techniques of resection and interposition have been described using stomach, jejunum or colon.

The stomach is technically the simplest organ to use for replacement, but when an end-to-end oesophagogastric anastomosis is used, reflux is not controlled and the risk of further ulceration and stricture formation reaches as high as 27 per cent within 6 months of resection[49]. This problem has been overcome in short segment replacement by adding a form of fundoplication[9] and in other cases by using a reversed gastric tube[50], although this seems to have been more widely used in children[51]. Interposition using an isoperistaltic segment of jejunum is technically more difficult, especially where long segment replacement is necessary, but good long-term results have been obtained by Polk with an operative mortality of 4 per cent but a significant incidence of early postoperative complications[52].

The most popular replacement organ has been an isoperistaltic segment of colon, which is suitable for long segment replacement, reaching as far as the neck if necessary. Its advocates claim that it is technically easier and safer to use than jejunum and more appropriate for use in childhood. The left colon based on the left colic artery is most often used. It has smaller bulk and its normal function is to transmit a solid bolus thus resulting in a better anatomical and functional result. However, ischaemic colitis and structural and functional problems more commonly affect the left colon and it is important to be assured of the vascularity and the absence of disease prior to its use. Belsey[53] has reported excellent results in a large series of colonic replacements with an operative mortality of 4·2 per cent and a low incidence of complications. The functional results of the colon as a replacement organ have been shown to be excellent[54].

Roux-en-Y duodenal diversion

This has been advocated in situations where bile is thought to be a major component of the refluxate or where previous multiple operations at the cardia make further dissection difficult. It is usually combined with antrectomy and vagotomy if feasible, such that both major reflux components are diminished and the risk of anastomotic ulceration reduced. Good results have been reported in these circumstances[55,56].

Reflux stricture is a serious complication of gastro-oesophageal reflux which demands active treatment to reduce the risk of permanent oesophageal damage. An accurate diagnosis is essential for effective management and when treated early, 95 per cent of strictures are dilatable. Resection can be avoided by combining dilatation with an effective anti-reflux procedure, together with gastroplasty where necessary. This is the management method of choice in patients with dilatable strictures who are fit for surgery, as surgery offers superior control to reflux and reduces the need for subsequent dilatations, with good results in over 75 per cent of patients. However, in frail, elderly patients in whom reflux is common, good symptomatic relief can be obtained with intermittent dilatation and medical anti-reflux measures. Resection remains necessary in approximately 5 per cent of patients who are resistant to more conservative methods or where multiple previous operations or motor disorders are an added problem. In these circumstances, colonic interposition is the preferred procedure, and is accompanied by good long-term and functional results. The small but definite risk of adenocarcinoma complicating reflux stricture must not be forgotten and careful follow-up of these patients is essential.

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Paper accepted 6 February 1987

Br. J. Surg. 1987, Vol. 74, June,
449–454

The future of external beam irradiation as initial treatment of rectal cancer

Several trials have demonstrated that pre-operative irradiation for rectal cancer decreases significantly the incidence of pelvic recurrence. However, this method is far from being generally accepted. It is now possible to enhance the effectiveness of external beam irradiation and to use it to extend the field of sphincter-saving and conservative procedures. Our protocol consists of a split-course regimen with a short course of cobalt-60 arc rotation (3000 cGy in 12 days). After 2 months rest, the second stage of treatment depends upon the pressure of residual disease and the site of the tumour. It consists of either radical surgery (82 cases) or conservative treatment by intracavitary irradiation in the event of a favourable initial response or in the case of poor risk patients (73 cases). In the radiotherapy–surgical group, the subsequent operative specimens were tumour free in 17 per cent of cases and assigned to Dukes' A category in 32 per cent of cases. Of 91 patients with T_2 or T_3 tumour involving the lower third of the rectum (followed up for more than 3 years) 72 (84 per cent) had no recurrence. Thirty-three of these patients (46 per cent) underwent a colostomy while 39 (54 per cent) had normal anal function. These results demonstrate the major place that a properly planned external beam irradiation can have in the curative management of cancers of the low rectum.

Keywords: Rectal cancer, radiotherapy, surgery, conservative treatment

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Optimal treatment of rectal cancer aims to give patients the best chance of cure while retaining normal anal function. Substantial progress has been made in the development of restorative procedures. However, tumours of the lower third of the rectum, which represent approximately 40 per cent of cancers of the rectum are usually treated by abdominoperineal resection, and have a poorer prognosis than those situated in the upper or middle third because of a higher rate of locoregional recurrences.

The results of radical surgery, whether abdominoperineal resection or low anterior resection, have not improved significantly during the past 30 years. The average 5 year survival rate remains fairly constant at about 50 per cent. Local recurrence is one of the principal causes of failure following surgery. The main purpose of pre-operative irradiation is not to alter the surgical procedure, but to improve the cure rate by increasing resectability rates and reducing the incidence of pelvic recurrences due to seeding at the time of surgery or the presence of cancer cells in the perirectal tissues. The decision to use pre-operative irradiation may be made on the basis of the clinical evaluation at the time of diagnosis.

Nicholls *et al.*[1] have shown that the clinician is able to assess the extent of palpable rectal cancers with satisfactory accuracy. Rectal carcinomas suitable for curative treatment may be divided into three general groups. The early or limited cancers are well differentiated adenocarcinomas not larger than 4 cm in diameter, freely mobile and confined to the bowel wall. For these cancers conservative treatment such as local excision, electrocoagulation or intracavitary irradiation may be an alternative to radical surgery. At the other extreme are advanced cases with large tumours deeply infiltrating the perirectal fat, some degree of stenosis of the rectal lumen and impaired mobility. Between these groups is an 'intermediate group' made up of tumours larger than 4 cm, moderately infiltrating, freely mobile and with little or no extrarectal spread. Currently, intermediate and advanced cases are treated by radical surgery, which is considered to be the only means of controlling the disease. However, in elderly poor risk surgical patients with intermediate tumours, it would be rational to try to avoid abdominoperineal resection by using external beam irradiation to convert the tumours into lesions amenable to conservative treatment.

The first important work devoted to pre-operative irradiation dates back to 1959 with the publication of a retrospective study from the Memorial Sloan–Kettering Cancer Center by Stearns *et al.*[2]. This report aroused much interest, and a large number of studies have since been published. Many of them are non-randomized, the figures are not convincing, and a bewildering variety of conclusions has been drawn[3–12]. Most studies have been conducted according to two principles: (1) homogeneous doses of radiation are distributed to large target volumes which include most, if not all, of the pelvic cavity. The tumour does not receive a higher dose than the surrounding normal structures. (2) Surgery is performed shortly after completion of irradiation.

When conservative treatment can be used in patients with rectal cancer it must be stressed that, regardless of the method employed (local excision, electrocoagulation or intracavitary irradiation), the approach is only applicable to selected patients with tumours less than 4 cm in size. At present these indications embrace less than 10 per cent of all patients with rectal cancer suitable for curative management, whereas more than 90 per cent of patients will undergo radical surgery[13,14].

The purpose of the present article is to evaluate a new protocol of external beam irradiation in the treatment of rectal cancer. Patient tolerance and treatment efficacy are assessed with particular reference to the possibility of avoiding abdominoperineal resection in favour of sphincter saving resection or conservative treatment.

Patients and methods

Radiotherapy technique

A particular treatment technique has been applied at the Centre Léon

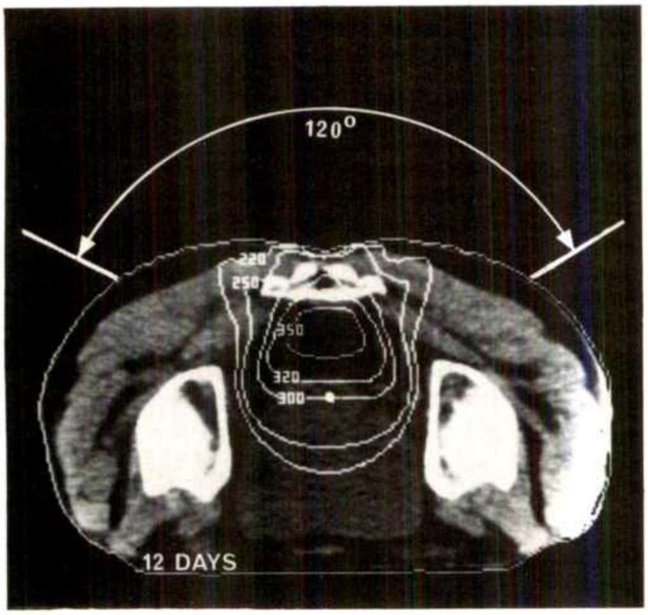

Figure 1 *Isodose distribution of pre-operative irradiation by cobalt-60 for cancer of the rectum. Irradiation is performed by 120° arc rotation through a 9 × 12 cm sacral field. The patient is in the prone position with full bladder. A dose of 3000 cGy calculated at isocentre which is at 10 cm depth is delivered in 10 fractions within 12 days. Note that a hot spot at 3500–3900 cGy is centred on the tumour area and that the target volume includes most of the posterior pelvic area with satisfactory protection of small bowel, urinary bladder and bony structures*

Bérard, Lyon, France since 1977, the main features of which are as follows[13,14].

(1) The target volume is limited yet includes the most important sites of regional spread of rectal cancer and the main lymphatic drainage areas of the rectum, especially the presacral area, the sidewalls of the posterior pelvic cavity, and the soft tissues anterior to the rectum. (2) Satisfactory protection of the urinary bladder and the small bowel is essential. (3) A short course of intensive irradiation delivers a minimum tumour dose of 3000 cGy in 10 fractions of 300 cGy within 12 days. The treatment starts on a Monday and ends on the Friday of the following week. This treatment is at least equivalent to a dose of 4500 cGy in 4·5 weeks. (4) A non-homogeneous dose distribution delivers a 20–30 per cent higher dose in the tumour area. (5) Surgery is not performed immediately following irradiation but after 2 months rest which allows optimal shrinkage of the tumour.

The irradiation is given by cobalt-60 using 120° arc rotation through a 9 × 12 cm sacral field and with the patient in the prone position. The dose of 3000 cGy is calculated at the isocentre which is 10 cm deep to the posterior surface. The isodose distribution shows that the tumour receives a dose of about 3500–3900 cGy (*Figure 1*).

One of the advantages of this method is its flexibility and the possibility of adapting the isodose distribution and its 'hot spot' to the site and spread of the tumour. This adaptation can be achieved by changing parameters such as the field size or the depth of axis of rotation. In very frail patients the overall treatment time may be protracted to 16 days by treating only four times a week.

The small bowel is protected by bladder distension, which displaces the small bowel anteriorly and superiorly. Patients are asked to drink as much water as possible 2 h before treatment and to keep a full bladder. Small bowel X-ray films are taken after opacification with barium sulphate, the patient being in the treatment position to simulate accurately the relative position of the small bowel with respect to the planned isodoses. Small bowel is excluded from the target volume.

Delaying operation for 8 weeks after completion of the short-term irradiation is a key factor in the method, because at this time the inflammatory phase following radiation has subsided, the fibrotic reaction has not begun and the optimal effect of the irradiation has been achieved. The clinician is able to take advantage of any tumour regression in assessing tumour spread and can make a more enlightened choice between radical, restorative and conservative treatment options.

Patients

This protocol of irradiation has been applied to 155 patients (median age, 69 years) who have now been followed up for periods of 6 months to 9 years (mean follow-up, 3 years). All patients were considered clinically to have resectable, biopsy proven T_2 or T_3 tumours of the rectum, that is tumours with involvement of muscle wall or serosa only (T_2), or tumours involving all layers with extension to immediately adjacent structures (T_3).

Patients given palliative treatment for unresectable or disseminated tumours were excluded from this study. The following results were observed in 82 patients who were subsequently operated on, and in 73 patients who were treated conservatively. The 82 operations consisted of abdominoperineal resection in 65 cases and low anterior resection in 17 cases. All operative specimens were examined to define the Dukes' grade of the tumour.

Patients were only selected for conservative treatment after radiotherapy if any of the following criteria were fulfilled:

(1) well or moderately well differentiated adenocarcinoma
(2) tumours of the lower third of the rectum which were too large (4–6 cm) or too close to the anus to be treated by intracavitary irradiation
(3) tumours which were mobile and moderately infiltrating in that there was little or no detectable extrarectal spread
(4) absence of palpable metastatic lymph nodes
(5) normal carcinoembryonic antigen (CEA) levels and CT scan
(6) patients considered to be high surgical risks because of their age or general condition
(7) limited residual disease detectable 2 months after completing external beam irradiation.

Results

Tolerance of radiotherapy

This radiotherapy course was well tolerated despite the advanced age of many of the patients. After irradiation, proctitis rarely lasts more than 3 weeks and responds rapidly to symptomatic management. There is no cystitis and no skin reaction in the sacral area. When the tumour is located close to the sphincter area, the perineal skin is included in the target volume, but its reaction is easily relieved by ointment. After this 3 week period, the symptoms related to the rectal tumour decrease and gradually disappear. After the 2 months rest most patients have gained weight and are in good condition.

Efficacy of radiotherapy

Of the 82 patients who underwent radical surgery, no technical difficulties were encountered in defining fascial planes or due to fibrosis or excessive bleeding related to the irradiation. In many cases the surgeon stated that the excision was especially easy. No particular delay in perineal wound healing was noted. Two patients (2·4 per cent) died within 30 days of operation. The efficacy of pre-operative irradiation was evaluated by the study of operative specimens and the status of patients followed up for more than 3 years. In 14 cases (17 per cent) the operative specimen was tumour free; this is the highest rate ever published. In 27 cases (33 per cent) the tumour was confined to the bowel wall. This high figure suggests that some Dukes' B tumours with extension through the serosa may have shrunk to become Dukes' A tumours. The relatively low incidence of Duke's C tumours (27 per cent) may be interpreted as due to the control of some metastatic lymph nodes.

Fifty patients treated by radiotherapy and surgery have been followed-up for more than 3 years; 42 underwent an abdominoperineal resection, eight a low anterior resection. Four patients died of intercurrent disease but were apparently cancer free, six developed distant metastasis but were locally controlled, four (8·3 per cent) died of local failure after total rectal excision. These figures demonstrate that the protocol can achieve the usual objective of pre-operative irradiation, namely a reduced incidence of pelvic recurrence after surgery (*Table 1*).

Extension of the applicability of restorative procedures

Of the 17 patients who underwent a low anterior resection, 10 had tumours within 6 cm of the anal verge. Operative specimens were tumour free in six cases (*Figure 2*), and allocated to Dukes' A, B and C categories respectively in five, four and two cases.

The apparent tumour regression following radiotherapy improved the prospects for a low anterior resection in 10 of these 17 cases, mostly with colo-anal anastomosis. Three patients had a diverting loop colostomy, which was closed after 3 months. Three patients developed anastomotic leakages; one following resection for a high located tumour, two after resection of low-lying lesions. These three patients underwent temporary colostomy which was closed 3–4 months later. No failure, either local or distant, occurred in these 17 patients. Of eight patients followed up for more than 3 years, one died within 30 days of operation while seven are still alive and apparently disease-free, three of them after colo-anal anastomosis for low-lying cancer.

Extension of the role of conservative treatment

In retrospect it can be argued that the 14 patients with tumour-free surgical specimens could have been spared radical surgery, and that some of the 27 patients with Dukes' A tumour could have been treated conservatively given that tumour regression was significant.

Table 1 *Outcome in 50 patients treated by pre-operative irradiation and radical surgery (minimum follow-up: 3 years)*

No. of cases	Alive and well	Dead of intercurrent disease	Dead of cancer or alive with cancer	Postoperative death
50	34 (68%)	4 (8%)	10 (20%)	2 (4%)

For patients unfit for surgery and for frail, poor surgical risk patients with low-lying tumours the usual choice lies between radical surgery and palliative treatment. The theoretical advantage of radical surgery may be offset by its mortality[15] and it is rational to consider a third option, namely concentrated irradiation followed by a wait of 2 months before a final decision is made about the most appropriate form of further treatment.

Seventy-three patients with T_2 tumours of the lower half of the rectum belonging to the 'intermediate group' were irradiated according to the above protocol. Their median age was 75 years. After 2 months rest the tumour shrinkage was substantial, the residual disease was limited and the great reparative capacity of the normal rectal mucosa was evident. In such cases abdominoperineal resection was abandoned in favour of a conservative procedure such as intracavitary irradiation (72 cases) or local excision and electrocoagulation (one case). Intracavitary irradiation was used to deliver a booster dose to the tumour bed to optimize local control. It consisted of one application of contact X-ray therapy with the 50 kV Philips machine to a dose of 2500 cGy and an iridium implant to a dose of 2000 cGy. Local excision was performed in one patient with residual tumour on the posterior wall in the sacral concavity and not easily accessible to intracavitary irradiation (*Figure 3*).

In this group of 73 patients treated conservatively but with curative intent, 45 have been followed up for more than 3 years.

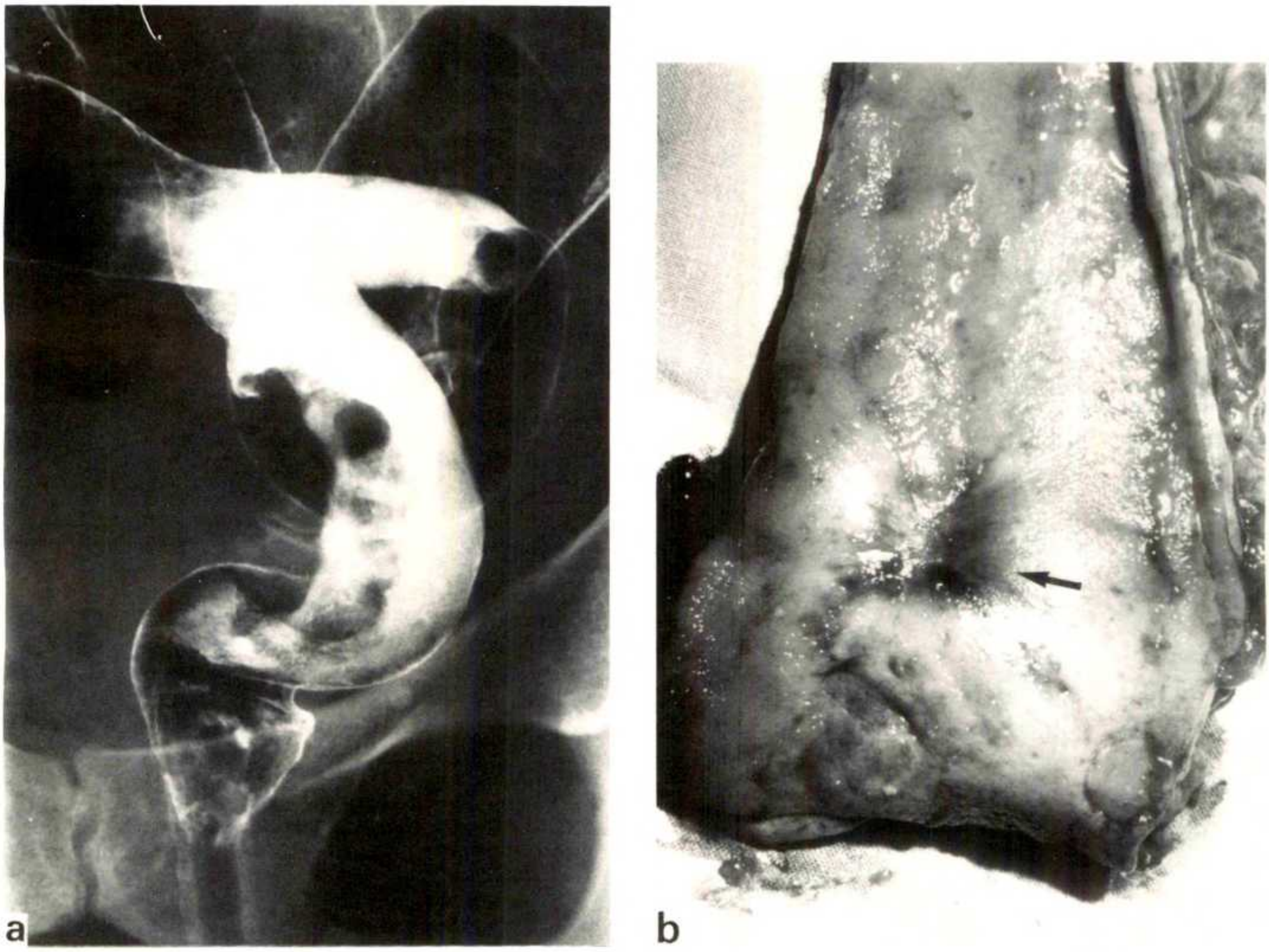

Figure 2 **(a)** *Female aged 44 years. Barium enema showing a bulky well differentiated adenocarcinoma 7 cm in length located 5–11 cm from the dentate line before pre-operative irradiation.* **(b)** *Same patient. Tumour-free operative specimen of low anterior resection 2 months after short course of irradiation. The tumour has disappeared and is replaced by a shallow ulceration. Patient alive and well 4 years after treatment*

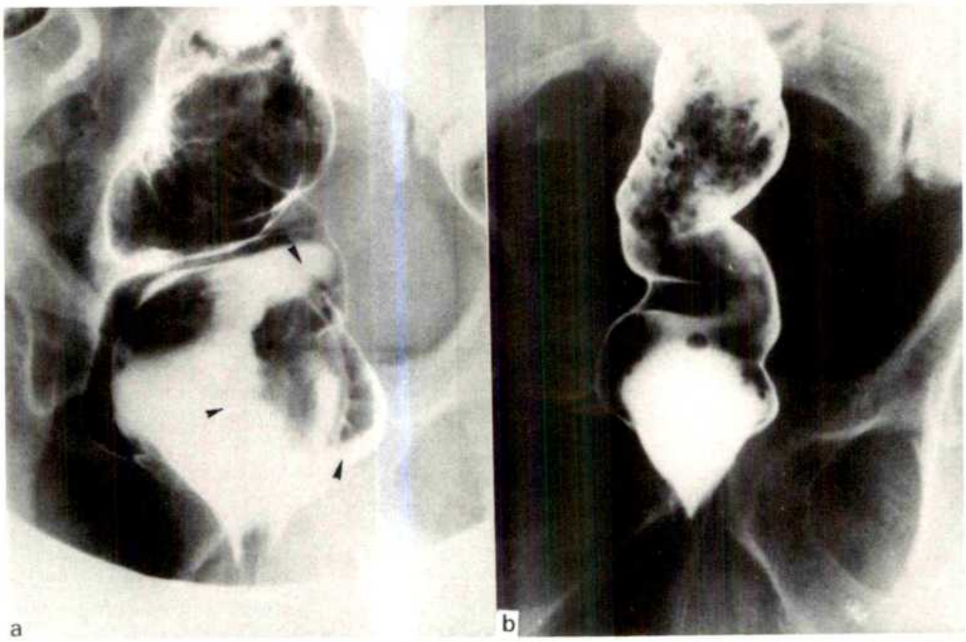

Figure 3 **a** *Male aged 60 years, poor surgical risk because of medical illness. Barium enema shows a bulky and ulcerative adenocarcinoma of the lower half of the rectum, 7 cm in length, located 3–10 cm from the dentate line before irradiation.* **b** *Same patient after split-course irradiation. The substantial shrinkage of tumour 2 months after a short course of irradiation allowed conservative treatment by intracavitary irradiation (Contact X-ray and iridium-192 implant). Patient clinically controlled 3 years after treatment.*

Table 2 *Results after conversion from radical into conservative treatment. Policy applied to 45 poor risk patients with moderately infiltrating cancer of the lower rectum (minimum follow-up: 3 years)*

No. of cases	Alive and well	Dead from intercurrent disease	Dead from cancer	Postoperative death
45	25 (55%)	13 (28·9%)	6 (13·3%)	1 (2·2%)

Table 3 *Overall results following external beam irradiation as initial treatment for T_2 and T_3 cancers involving the lower third of the rectum (minimum follow-up: 3 years)*

No. of cases	Alive and well	Dead from intercurrent disease	Dead from cancer	Postoperative death
91	55 (60·4%)	17 (18·7%)	16 (17·6%)	3 (3·3%)

The results are reported in *Table* 2. Of eight patients (17·8 per cent) who developed local failure, three are alive and well after subsequent abdominoperineal resection (2) or electrocoagulation (1), one aged 84 died within 30 days of operation, and four died from cancer (three of them were deemed inoperable because of their general condition). Two patients died from distant metastasis but were locally controlled. Thirteen (28·9 per cent) died from intercurrent disease. This high figure reflects the advanced age of patients. Twenty-five patients are alive and well after 3–8 years of follow-up, 23 with normal anal function, and as previously mentioned, two after salvage surgery. Of these 45 patients, the disease has been controlled in 36 (80 per cent) with preservation of a normal anal sphincter (*Figure 3*).

During the first years of this study only elderly patients were accepted into this extension of conservative treatment. Analysis of the results prompted us to enlarge the indications during the past 2 years to middle-aged, good risk patients. To answer possible criticism concerning the question of lymphatic spread, three patients underwent an inferior mesenteric and extramesenteric lymphadenectomy. This operation, initiated at the Centre Léon Bérard[13,16], aims to check the main lymphatic drainage areas of the rectum and to explore the pelvis without bowel excision. The operation was performed 3 months after control of the primary tumour had been achieved. No involved nodes were found and all these patients are clinically well.

Overall outcome

Of the 95 patients followed up for more than 3 years, 4 had tumour located in the upper two-thirds of the rectum suitable for restorative surgery and 91 had T_2 or T_3 tumours of the lower third of the rectum treated either by radiotherapy and surgery (46) or by conservative method (45). Fifty-five (60·4 per cent) are alive and well, 17 died of intercurrent disease but were cancer-free; 16 (17·6 per cent) died of cancer (*Table 3*). No patients were lost to follow-up. Among the 72 patients who had no failure, neither local nor distant, 39 (54·1 per cent) had no colostomy.

Discussion

The revival of interest in radiotherapy in the management of rectal cancer is due to the increased effectiveness of irradiation of a tumour which, 25 years ago, was considered to be radioresistant. Among the numerous studies devoted to pre-operative irradiation, the most informative is the second trial of the European Organization for Research on Treatment of Cancer in which 318 patients were randomized to receive 3450 cGy in 19 days pre-operatively, or surgery alone. In the radiotherapy group, operation was performed 2 weeks after the completion of irradiation. The results published by Gerard *et al*[17] showed that 85 per cent of patients were free of local recurrence at 5 years after radiotherapy as opposed to only 65 per cent in the surgery alone group ($P = 0{\cdot}001$). There is also a significant difference in the survival between the two treatment groups, and the percentage of patients disease free at 5 years is 70 per cent for the radiotherapy group *versus* 60 per cent for the control group ($P = 0{\cdot}032$). It must be noted that in this trial 13 per cent of patients underwent a restorative procedure, 81 per cent an abdominoperineal resection and 6 per cent other surgical procedures. These figures contrast with those of the

Rectal Cancer Group reported by Porter and Nicholls[18] who cited a 52·9 per cent incidence of anterior resection, showing the recent progress made in the development of sphincter-saving procedures. However, in almost all studies of combined treatment the irradiation does not interfere with the surgery and the type of operation is only chosen according to the site and spread of the tumour and to the local and general conditions at the time of surgery.

In spite of technical progress, pelvic recurrence remains the main cause of treatment failure after restorative surgery. The incidence of locoregional recurrences is mainly related to the distance of the primary tumour from the dentate line. In the Mayo Clinic experience[19], this rate is 9 per cent for tumours located between 8 and 10 cm from the dentate line and 22·2 per cent for low-lying lesions. In the same institution the rates are between 10 and 26 per cent according to the suture technique[20]. The results obtained by combining irradiation and abdominoperineal resection may strengthen the case for pre-operative radiotherapy before restorative surgery in order to decrease the rate of pelvic failure. However, the fear of increased postoperative morbidity, particularly anastomotic leakage, has deterred many surgeons from using external beam irradiation before anterior resection for tumours of the upper and middle thirds of the rectum. They consider that the safety of an intestinal anastomosis in irradiated bowel has not yet been established.

Nicholls[21] has highlighted the high incidence of anastomotic leakage after surgery alone when the anastomosis is made below the peritoneal reflection. The frequency ranges from 5 to 30 per cent of cases. The literature contains only relatively limited statistics on patients who have actually received adequate doses of pre-operative irradiation. After pre-operative irradiation the rates of anastomotic leaks vary from 0[22] to 20 per cent[23] and 22 per cent in the experience of Stevens *et al.*[24], who advised protective colostomies. Roberson *et al.*[22] conducted a study of 40 patients treated for rectal cancer with 4500 cGy over 5 weeks followed within 1–3 weeks by low anterior resection. Fourteen of the forty patients with low-lying tumours had diverting colostomies performed because of difficult anastomoses. There were no clinical anastomotic leaks and no postoperative deaths. In a median follow-up of 44 months one patient had local recurrence. Factors thought to favour reduction of anastomotic leakage were close collaboration between surgeons and radiotherapists, limited target volume of irradiation and meticulous surgical technique. These data demonstrate that colorectal anastomosis is possible after irradiation to 4500 cGy without serious complications but, in selected cases, a diverting colostomy is still advisable. At the Centre Léon Bérard, the present tendency is to advise a protective colostomy for most patients with very low tumours in whom the surgeon took advantage of tumour shrinkage to extend the indications for sphincter preservation. For tumours of the upper or middle third of the rectum, it is advisable to extend the fractionation so that the overall treatment time of irradiation is no shorter than 16 days.

The irradiation used at the Thomas Jefferson University Hospital, Philadelphia, USA[25,26] and at the Centre Léon Bérard, Lyon[13,14] aims not only to improve the long-term results after surgery but also to convert some low tumours into lesions amenable to restorative surgery. Marks *et al.*[26] reported 24 patients with tumour located more than 3 cm from the dentate line who were treated with 4500 cGy followed by an abdominotrans-sacral resection and proximal transverse colostomy. One patient sustained an anastomotic leakage and no pelvic recurrences were observed.

The last area for discussion concerns the possible control of rectal tumours by irradiation alone. In many series of combined radiotherapy and surgical management, some tumour-free operative specimens have been reported[11,12,17,23,24,26,27]. The high rate of tumour-free operative specimens in the series of Stevens *et al.*[24] is explained both by the high dose of radiation (5000 cGy) and the interval of 4–7 weeks between the completion of irradiation and the surgery.

Wang and Schulz[28] in 1962 were among the first to report cure at 5 years after irradiation therapy alone and considered that 6 of their 58 inoperable patients may have been cured in this way. Rider *et al.*[29] and Cummings[30] showed that protracted irradiation is able to control mobile rectal tumours in 38 per cent of cases. They emphasized that the tumour response is particularly slow and that an early decision may be inadequate. The present series corroborates these data, but the technique of irradiation used in our centre is quite different from those previously employed. When assessed 6–8 weeks after the completion of treatment the effectiveness of a short but intensive course of irradiation is greater than expected. The tumour response allows the most appropriate approach to be selected for each patient.

The low rate of local failures after surgery among patients followed up more than 3 years, and the results obtained in patients with low-lying tumours treated either by sphincter preserving surgery or by irradiation alone support a plea for external beam irradiation as the initial treatment in most cases of non-obstructive rectal cancers suitable for curative management. The results in terms of the extension of the role of restorative surgery and of conservative treatment are encouraging. It is now possible to spare a larger number of elderly patients a permanent colostomy without jeopardizing their chance of cure.

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Paper accepted 11 February 1987

Announcement

Overseas Doctors Training Scheme (Surgery)

At the request of the Department of Health and Social Security (DHSS), the Royal College of Surgeons of England is setting up a training scheme in general surgery and orthopaedics for doctors from abroad. This will be under the arrangements for double sponsorship introduced by the General Medical Council. The posts included in the scheme will be established National Health Service posts subject to the DHSS Terms and Conditions of Service and with Royal College recognition. In the main overseas doctors will be appointed to rotational programmes of surgical training, where possible including University Teaching Hospitals, in regions throughout England and Wales, and Northern Ireland. The principle aim of this scheme is to provide a high standard of surgical training for doctors outside the United Kingdom and the European Community to help them in their work when they return home. Further particulars can be obtained from the ODTS office, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK.

Br. J. Surg. 1987, Vol. 74, June, 455–459

External beam radiotherapy for rectal adenocarcinoma

A series of 243 patients with adenocarcinoma of the rectum treated with radiotherapy is presented. In the early part of the study radiotherapy was combined with 5-fluorouracil (5FU). Later, radiotherapy was given alone. Seventy-four patients were treated with radical external beam radiotherapy for recurrent or inoperable rectal adenocarcinoma. One hundred and forty-five patients with advanced pelvic tumours or with metastases were treated with palliative pelvic radiotherapy. Twenty-four patients who had small-volume residual pelvic tumour or who were felt to be at high risk of pelvic recurrence following radical resection received postoperative radiotherapy. Complete tumour regression was seen in 38 per cent of radically treated patients, and 24 per cent of palliatively treated patients. Partial regression was observed in 56 per cent of radically treated patients, and 58 per cent of palliatively treated patients. Long-term local tumour control was more commonly observed for small tumours (<5 cm diameter). Fifty-eight per cent of patients treated with postoperative radiotherapy remained free of local recurrence. Survival was significantly better in patients with small tumours. The addition of 5FU did not appear to improve survival or tumour control. The value of radiotherapy in the relief of distressing symptoms related to the presence of pelvic tumour has been confirmed.

Keywords: Rectum, adenocarcinoma, radiotherapy

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Radical surgery is the treatment of choice for adenocarcinoma of the rectum[1]. Primary radical radiotherapy has been advocated as an effective treatment for patients presenting with tumours that are inoperable owing to invasion of surrounding pelvic organs, or with concomitant cardiovascular or respiratory disease precluding radical surgery[2,3].

Patients presenting with advanced pelvic tumours not amenable to radical radiotherapy frequently experience distressing symptoms, particularly rectal bleeding, mucoid discharge or pain. Palliative pelvic radiotherapy has been reported to provide complete or partial symptomatic relief in approximately 60–70 per cent of these patients[2–5].

Following radical surgery, residual pelvic disease is left in a proportion of patients. Others have a high risk of local recurrence owing to histological evidence of tumour at the resection margin, or difficulty in resecting the tumour. It has been suggested that these patients might benefit from postoperative radiotherapy.

A series of patients with rectal adenocarcinoma treated with radical external beam radiotherapy for inoperable disease or recurrence, with postoperative radiotherapy for residual pelvic tumour or a high risk of recurrence, or palliatively have been reviewed to evaluate the symptomatic benefit of radiotherapy, as well as local control and survival.

Patients and methods

Between January 1974 and December 1983, 243 patients with adenocarcinoma of the rectum were treated with radiotherapy. Seventy-four patients with inoperable or recurrent rectal adenocarcinoma were treated with radical external beam radiotherapy. A further 24 with residual pelvic tumour, or a high risk of recurrence following radical resection were treated with postoperative radiotherapy. An additional 145 patients received palliative pelvic radiotherapy. Patient details are given in *Table 1*. Excluded from the analysis are patients who entered a randomized trial comparing neutrons with photons[6] and those who entered the first Medical Research Council (MRC) trial of pre-operative radiotherapy.

Radiotherapy techniques and doses

Patients were treated with megavoltage radiotherapy using a 4 MeV or 9 MeV linear accelerator. A variety of field arrangements, sizes and radiation doses were employed.

Radical radiotherapy. The majority of patients were treated with three or four-field beam-directed techniques. Field sizes varied from 12 × 10 cm to 18 × 15 cm. Patients were treated daily either continuously (54 patients) or with a 'split course' (20 patients). The majority of patients treated with a continuous course received a dose of 45–55 Gy in 20 fractions over 4 weeks, and for split course, 30–35 Gy in 10–15 fractions daily over 2–3 weeks followed 4 weeks later by 30–35 Gy in 10 fractions over 2 weeks.

Postoperative radiotherapy. The majority of patients were treated with parallel-opposed or beam-directed techniques, using field sizes

Table 1 *Distribution of patients*

Total number of patients	243
Male	130
Female	113
Mean age in years (range)	66 years (28–91)
Radical radiotherapy	
Recurrent following surgery	33
Inoperable owing to extent of tumour in pelvis	30
Inoperable owing to age or concomitant medical condition	11
Postoperative radiotherapy	
Residual pelvic tumour	14
Adjuvant (high risk of recurrence)	10
Palliative radiotherapy	
Without metastases at presentation	66
With metastases at presentation	79

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similar to radically treated patients, giving doses of 45–50 Gy in 20 fractions over 4 weeks.

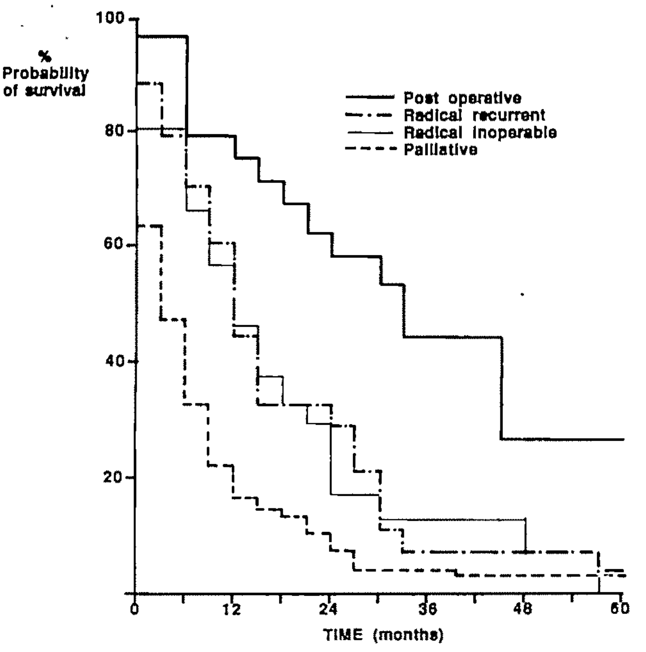
Palliative radiotherapy. The majority of patients were treated with parallel-opposed fields, with sizes varying from 12 × 10 cm to 20 × 15 cm. Most patients received a radiation dose of 30–35 Gy in 10 fractions over 2 weeks. However, 18 patients received a one-week course, and 3 patients a single fraction of radiotherapy.

Chemotherapy

Between 1974 and 1977, 46 patients (radical: 16, palliative: 30) received 5FU 250 mg IV daily following each fraction of radiotherapy.

Tumour size

For patients treated with radical and palliative radiotherapy, assessment of tumour size was made, based on either measurements recorded prior to radiotherapy or descriptions of laparotomy findings. For 31 patients an assessment of size could not be made.



Time (months)	6	12	18	24	30	36	42	48	54	60
Postoperative ($n=24$)	23	19	17	14	13	8	5	3	3	3
Radical recurrent ($n=33$)	28	19	10	10	6	2	2	2	2	1
Radical inoperable ($n=41$)	33	22	14	10	5	3	2	2	1	–
Palliative ($n=145$)	67	32	21	14	6	5	3	3	3	2

Figure 1 *Overall actuarial survival in 243 patients subdivided by the treatment categories*

Pathological grade

Fifty-two patients (21 per cent) had well-differentiated, 66 (27 per cent) moderately differentiated, and 40 (17 per cent) poorly differentiated tumours. For 85 patients (35 per cent) the grade was not stated.

Statistical methods

Survival time was measured from the date of the first radiotherapy treatment. Actuarial survival was calculated using the life-table method (excluding deaths from intercurrent disease) and survival rates compared using the Logrank test[7].

Tumour response

Complete response was defined as complete regression of all clinically detectable disease. Partial response was defined as clear objective evidence of tumour regression following radiotherapy. Recorded measurements of tumour size following radiotherapy were not sufficiently precise to employ a more strict definition of partial response.

Results

Overall survival

Actuarial survival for the different treatment groups is given in *Figure 1*. Actuarial survival at 1, 2 and 5 years and numbers of deaths due to rectal carcinoma and intercurrent disease are given in *Table 2*.

There was a significant ($P < 0.001$) survival advantage for patients with small tumours (*Figure 2*), but histological grade did not significantly influence survival ($P = 0.116$).

Tumour response

For 141 patients, tumour response could be assessed, and the proportions of patients with objective tumour response are given in *Table 3*. For 55 evaluable patients treated radically 21/55 (38 per cent) achieved complete response, 31/55 (56 per cent) partial response and 1/55 (2 per cent) no response, and for 62 evaluable patients treated palliatively 15/62 (24 per cent) achieved complete response, 36/62 (58 per cent) partial response and 11/62 (18 per cent) showed no response.

Tumour response according to size of tumour is given in *Table 4*. Of 9 radically treated patients with tumours < 5 cm diameter achieving complete response, 6 remained free of local recurrence, and 3 relapsed locally. Of 11 radically treated patients with tumours greater than 5 cm diameter achieving complete response, 8 later relapsed locally, 2 remained free of local recurrence, and one was not assessable.

Patients achieving complete response had a significantly better survival than the remainder (*Figure 3*). There was little difference in survival between partial and non-responders.

Influence of 5FU

There was no significant difference in survival ($P = 0.705$) or tumour response for patients treated with combined 5FU and radiation compared with those treated by radiation alone.

Table 2 *Actuarial survival and cause of death*

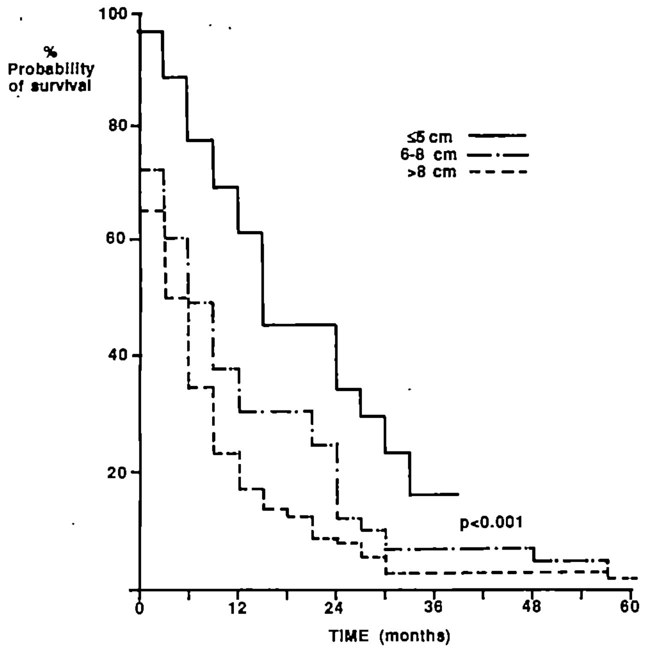
	Actuarial survival (%)			Cause of death	
	1 year	2 years	5 years	Rectal carcinoma	Intercurrent disease
Radical					
Recurrent	60	32	4	30	1
Inoperable owing to disease extent	57	20	0	28	1
Inoperable owing to age/condition	55	55	0	7	3
Postoperative					
Residual disease	71	41	—	11	1
Adjuvant	90	90	59	5	—
Palliative	22	10	3	142	2

Symptomatic response

One hundred and seventy-five patients (radical: 58, palliative: 117) were evaluable for symptomatic response. Details of response of major symptoms are given in *Tables 5* (radical) and *6* (palliative). Overall symptomatic response for radically treated patients was 75 per cent (complete: 44 per cent, partial: 31 per cent) and for palliatively treated patients was 77 per cent (complete: 30 per cent, partial: 47 per cent).

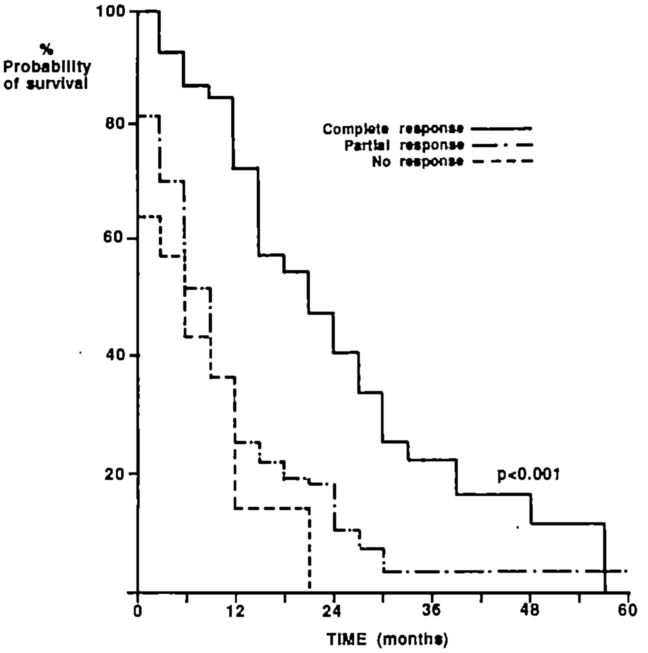
Postoperative radiotherapy

Lasting local control was achieved in 6 of the 10 patients with histological evidence of tumour at the resection margin, or with



Time (months)	6	12	18	24	30	36	42	48	54	60
≤5 cm (*n*=28)	23	18	11	9	5	2	–	–	–	–
6–8 cm (*n*=43)	26	15	12	10	4	3	3	3	2	1
≤8 cm (*n*=121)	60	28	17	11	7	4	4	4	4	2

Figure 2 *Actuarial survival – influence of tumour size*



Time (months)	6	12	18	24	30	36	42	48	54	60
Complete response (*n*=37)	34	29	19	14	9	5	3	3	2	–
Partial response (*n*=67)	47	24	15	12	5	2	2	2	2	2
No response (*n*=14)	8	5	2	–	–	–	–	–	–	–

Figure 3 *Actuarial survival – influence of tumour response*

Table 3 *Tumour response*

Treatment category	Number of patients	Response: Complete (%)	Partial (%)	None (%)	Not assessable (%)
Radical					
Recurrent	33	9 (27)	11 (33)	2 (6)	11 (33)
Inoperable owing to disease extent	30	6 (20)	16 (53)	1 (3)	7 (23)
Inoperable owing to age/general condition	11	6 (55)	4 (36)	—	1 (9)
Palliative	145	15 (10)	36 (25)	11 (8)	83 (57)

Table 4 *Tumour response according to size*

	Number of patients	Response: Complete (%)	Partial (%)	None (%)	Not assessable (%)
Radical					
Tumour size (cm)					
<5	16	9 (56)	4 (25)	—	3 (19)
6–8	22	6 (27)	10 (45)	2 (9)	4 (18)
>8	25	5 (20)	15 (60)	1 (4)	4 (17)
Not recorded	11	1 (9)	2 (18)	—	8 (73)
Palliative					
Tumour size (cm)					
<5	10	5 (50)	3 (30)	—	2 (20)
6–8	21	4 (19)	4 (19)	2 (10)	11 (52)
>8	96	5 (5)	28 (29)	9 (9)	54 (57)
Not recorded	18	1 (6)	1 (6)	—	16 (89)

Table 5 *Radical radiotherapy – symptomatic response*

Symptoms	Number of patients	Response			
		Complete (%)	Partial (%)	None (%)	Not assessed (%)
Pain	37	23 (62)	11 (30)	2 (5)	1 (3)
Rectal bleeding	28	25 (89)	—	—	3 (11)
Mucoid discharge	22	7 (32)	12 (55)	2 (9)	1 (4)
Diarrhoea	13	6 (46)	5 (38)	1 (8)	1 (8)
Overall symptomatic control	74	33 (44)	23 (31)	2 (3)	16 (22)

Table 6 *Palliative radiotherapy – symptomatic response*

Symptoms	Number of patients	Response			
		Complete (%)	Partial (%)	None (%)	Not assessed (%)
Pain	73	27 (37)	36 (49)	2 (3)	8 (11)
Rectal bleeding	46	29 (63)	10 (22)	2 (4)	5 (11)
Mucoid discharge	50	17 (34)	26 (52)	3 (6)	4 (8)
Diarrhoea	21	6 (29)	11 (52)	2 (9·5)	2 (9·5)
Overall symptomatic control	145	43 (30)	68 (47)	6 (4)	28 (19)

tumours that had been resected with difficulty. Four are alive and disease free at 48–80 months, and one is alive with local recurrence 42 months after adjuvant radiotherapy. Five have died of local recurrence or metastatic disease. Lasting local control was achieved in 8 of the 14 given postoperative radiotherapy for residual pelvic tumour, 2 are alive and disease free at 33 and 36 months, 2 have died of intercurrent disease, and 10 have died of local recurrence or metastatic tumour.

Toxicity

Details of early and late toxicity were available for 238 patients (radical: 70, palliative: 144, postoperative: 24). Radiotherapy was generally well tolerated, with no toxicity seen in 13/70 (19 per cent) given radical radiotherapy, 88/144 (61 per cent) given palliative radiotherapy, and 3/24 (12·5 per cent) given postoperative radiotherapy. Diarrhoea or tenesmus was seen in 79 per cent of patients given postoperative radiotherapy, 56 per cent of radically treated and 31 per cent of palliatively treated patients. However, in the majority this was mild and good symptomatic improvement was obtained with codeine phosphate or diphenoxylate (Lomotil), or steroid suppositories. Nausea, vomiting, skin erythema and dysuria were seen in a minority of patients. Four of sixteen patients treated with combined 5FU and radical radiotherapy developed vomiting or diarrhoea sufficiently severe to require IV fluids. Haematological toxicity was seen in 6/46 (13 per cent) patients treated with 5FU but was not severe.

Late radiation toxicity, either bowel stricture or perforation, or perineal ulceration was seen in 8 patients, but was severe requiring surgery in only 4.

Discussion

Although radical surgery remains the treatment of choice for rectal adenocarcinoma[1], a proportion of patients will present with tumours that are inoperable owing to local pelvic extension, or will have concomitant cardiovascular or respiratory disease precluding radical surgery. The results of this series confirm the potential of radical radiotherapy for local tumour control[2,3].

Small tumours (< 5 cm diameter) were most likely to regress completely following radiotherapy, and it was in the group of patients with disease that was inoperable owing to concomitant general medical conditions that these small tumours were seen. Of the 9 patients with tumours < 5 cm diameter which regressed completely following radical radiotherapy, 6 remained free of local recurrence compared with only 2 of the 10 assessable patients with tumours greater than 5 cm diameter which regressed completely following radical radiotherapy.

Examination of this series of patients demonstrates clearly that in those patients who have small, technically operable tumours, but who have other medical conditions making radical surgery unsafe, radical radiotherapy offers a useful alternative with a good chance of local tumour control.

Although long-term local control is likely only for small tumours, a high proportion of patients with larger lesions (6–8 cm diameter) which can be encompassed in a radical radiation field will gain significant relief of symptoms. An attempt to give radical rather than palliative radiotherapy should always be made if the patient's general condition allows, since the chance of complete symptomatic control is greater for radically treated compared with palliatively treated patients.

Inoperable tumours that regress following radiotherapy may be rendered operable. In a recent series of 42 patients with fixed inoperable rectal carcinomas treated with moderate doses of external beam radiotherapy, 18 subsequently had a radical resection performed[8].

As in other series[2–5], for patients with advanced pelvic tumours too extensive to treat with radical radiotherapy, and for those presenting with metastases, palliative radiotherapy provided useful symptomatic improvement in 77 per cent of patients. Rectal bleeding was most likely to respond well to radiotherapy, but useful responses of mucoid discharge, pain and diarrhoea were also seen.

The survival of palliatively treated patients was poor, with only 47 per cent alive at 6 months and 22·5 per cent alive at one year. When considering palliative radiotherapy it is important to take the patient's general condition into account, and exclude patients with very advanced tumours and short life expectancy who are unlikely to benefit from treatment.

Pelvic radiotherapy was generally well tolerated. However, the predominant toxicity was lower gastrointestinal, mainly tenesmus due to radiation proctitis and watery diarrhoea. In the majority of patients these symptoms responsed well to routine medication.

5FU is an antitumour antimetabolite with a response rate of approximately 21 per cent in patients with rectal adenocarcinoma[9]. Early experimental work demonstrated radiosensitizing properties[10] and its potential for improving tumour control when combined with radiation is being investigated. In this study, there was no evidence of either survival advantage or improved tumour control in patients treated with combined radiation and 5FU given this way. In addition, patients treated with combined therapy were more likely to experience severe gastrointestinal toxicity.

The value of postoperative radiotherapy for sterilizing small-volume macroscopic residual pelvic tumour has been demonstrated, with 8 of 14 patients remaining free of local recurrence. Six out of ten patients with histological evidence of tumour at the resection margin or in whom resection was difficult remained free of local recurrence. It is likely that the majority would have developed local pelvic recurrence without postoperative radiotherapy. In a randomized trial, the Gastro-Intestinal Tumour Study Group has demonstrated prolongation of disease-free survival following postoperative radiotherapy for surgically treated rectal carcinoma[11], and the role of postoperative radiotherapy for Dukes' B and C rectal carcinoma is currently the subject of an MRC multicentre trial[12].

Radical radiotherapy was found to be most effective for controlling small tumours in this group of patients. For small low-lying tumours, a different approach using localized high dose radiotherapy given by an endocavitary source via a proctoscope appears to provide an excellent chance of local control, avoiding the need for abdominoperineal resection[13], and its role should be evaluated further.

In conclusion, this study has demonstrated the potential of radical radiotherapy for achieving tumour control in patients with recurrent and inoperable rectal adenocarcinoma, particularly those with small tumours, but who have severe cardiovascular or respiratory disease precluding radical surgery. For those who present with advanced pelvic tumours or metastases, radiotherapy provides effective palliation of the major symptoms, particularly rectal bleeding, pain and mucoid discharge. Postoperative radiotherapy appears effective for patients who have residual small-volume pelvic tumour or who are felt to have a high risk of recurrence following resection.

Acknowledgements

We thank the surgeons in the area for referring the patients. We are grateful to Mrs Irene Noble for typing the manuscript.

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Paper accepted 6 February 1987

Br. J. Surg. 1987, Vol. 74, June, 460–463

Role of urokinase in colorectal neoplasia

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The biofunctional activity of the plasminogen activators urokinase and tissue plasminogen activator has been measured in extracts from 50 colorectal carcinomas and 21 adenomas using a bioimmunoassay. Compared with control mucosa urokinase activity was significantly elevated in adenomas ($P<0{\cdot}001$) *and carcinomas, levels being significantly higher in carcinomas* ($P<0{\cdot}05$). *In contrast tissue plasminogen activator activity was reduced in adenomas* ($P<0{\cdot}01$) *and carcinomas, levels being significantly lower in carcinomas* ($P<0{\cdot}01$). *Although enzyme activity did not relate to Dukes' stage or histological grade urokinase activity was higher in carcinomas with venous invasion* ($n=17$, $P<0{\cdot}05$), *in those with moderate or extensive local spread* ($n=27$, $P<0{\cdot}05$) *and in cases where a palliative resection only was feasible because of advanced disease* ($n=8$, $P<0{\cdot}05$). *Urokinase has been implicated in tissue degradation as well as fibrinolysis and may play a role in tumour invasion and metastasis in human colorectal neoplasia.*

Keywords: Colorectal neoplasia, urokinase, invasion, metastasis

Recent studies have highlighted the association of proteolytic enzymes with malignant tumours[1–3] suggesting that they may play a role in tumour invasion. Although the fibrinolytic system has been particularly associated with tumour metastasis[4,5], plasmin, a tryptic enzyme which can degrade a variety of extracellular components[6] other than fibrin, is also implicated in local invasion. This protease is generated from its inactive precursor, plasminogen, by the action of plasminogen activators, enzymes which exist in two well characterized forms as urokinase and tissue plasminogen activator. In a recent report we confirmed a marked increase in biofunctional urokinase activity in colorectal carcinomas compared with normal colorectal mucosa and further demonstrated a similar trend in urokinase activity in adenomas[7].

In this study specific biofunctional urokinase and tissue plasminogen activator activity has been further investigated and related to stage and histopathological grade as well as to the presence of venous invasion and degree of local spread in colorectal carcinomas. Enzyme activity in the carcinomas was also assessed in relation to whether the resection was considered to be curative or palliative and has been further compared with that in adenomas.

Patients and methods

Fresh tissue was obtained from 50 resected specimens of colorectal carcinoma (23 women and 27 men; median age 64 years, range 40–86 years) and from 21 adenomas (11 women and 10 men; median age 68 years, range 51–86 years). Sixteen adenomas were sampled after colonoscopy and five after surgery. Samples of non-necrotic tumour and of macroscopically normal mucosa taken distant from the carcinomas, were thoroughly washed in phosphate buffered saline containing azide, blotted dry, flash frozen in liquid nitrogen and stored at −70°C. Weighed portions from each sample were then homogenized in phosphate buffered saline containing sodium azide as previously described[7]. After ultracentrifugation the supernatants were assayed by bioimmunoassay[8]. This procedure depends on the binding of plasminogen activator in the sample to the immobilized IgG fraction of a rabbit antisera raised against urokinase or tissue plasminogen activator respectively, with the subsequent activation of added plasminogen. The plasmin so generated was detected using a chromogenic substrate (S2251 Kabi Vitrum). The results, read as optical density, were calibrated from dilution curves using the WHO standards of tissue plasminogen activator or urokinase accordingly and expressed in international units per millilitre of a standardized homogenate (units/ml). The interassay geometric coefficient of variation was 5·8 per cent[8].

Carcinomas were classified by standard histopathological criteria and further subdivided according to the extent of local spread and to the presence or absence of histological evidence of venous invasion by one independent observer. In this study moderate and extensive degrees of local spread were combined and have been compared with cases without or with minimal local spread. Carcinomas with moderate and extensive local spread had evidence of tumour penetration of at least 5 mm, either continuous or discontinuous, beyond the muscularis propria as measured using an eyepiece micrometer. In 35 cases local spread was assessed after multiple full thickness transverse sectioning through the gross specimen. Venous invasion referred only to the involvement of extramural veins. Patients were additionally grouped as having undergone either a curative resection or a palliative resection due either to distant metastases or residual local disease.

The data were non-parametric and, therefore, have been presented as medians (range) and analysed using the Mann–Whitney *U* test (one tailed) for unpaired, Wilcoxon rank sum test for paired data and the Spearman rank test.

Results

There was no relationship in control mucosa between either urokinase ($r_s=0{\cdot}14$, n.s.) or tissue plasminogen activator activity ($r_s=0{\cdot}01$, n.s.) and age, neither did enzyme activity in control mucosa from women differ from that in men (median activities, men *versus* women; urokinase 0·2 *versus* 0·3; tissue plasminogen activator 4·2 *versus* 3·5). The distribution of urokinase and tissue plasminogen activator activity in colorectal neoplasms and control mucosa is demonstrated in *Figures 1* and *2*. Urokinase activity was significantly elevated in both adenomatous polyps ($P<0{\cdot}001$) and carcinomas ($P<0{\cdot}001$), levels being highest in carcinomas ($P<0{\cdot}05$), compared to the low levels in control mucosa. The ratios of median urokinase activities in carcinomas and polyps to control mucosa were 4·5 and 2·2 respectively. In contrast tumours had reduced tissue plasminogen activity compared with control mucosa ($P<0{\cdot}001$), levels being lowest in carcinomas ($P<0{\cdot}01$). The ratios of median tissue plasminogen activator activities of carcinomas and polyps to normal mucosa respectively were 0·2 and 0·4. There was no relationship between tissue plasminogen activator or urokinase activity and either Dukes' histopathological stage or grade of differentiation.

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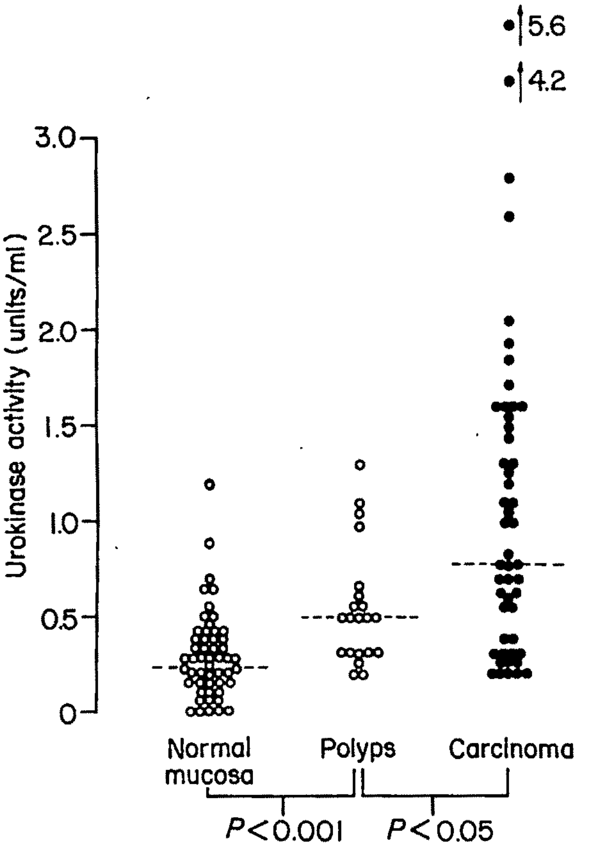

Figure 1 *Urokinase activity in control colorectal mucosa, adenomatous polyps and colorectal carcinomas*

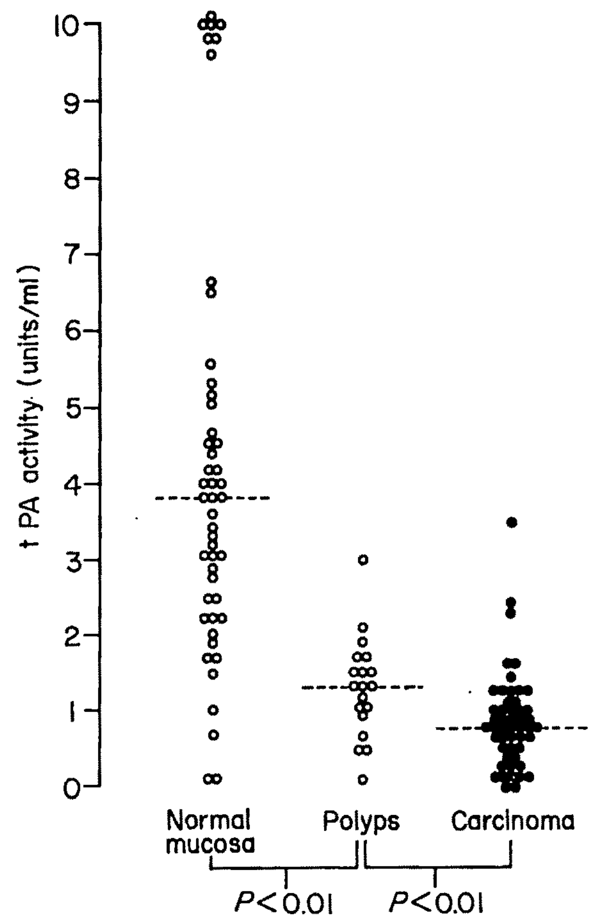

Figure 2 *Tissue plasminogen activator (tPA) activity in control colorectal mucosa, adenomatous polyps and colorectal carcinomas (19 polyps only were assessed for tissue plasminogen activity)*

In 27 carcinomas with moderate or extensive local spread, urokinase activity was greater than in those with minimal or without local spread (median values 1·1 units *versus* 0·7 units respectively; $P < 0{\cdot}04$, *Figure 3*). The same pattern was observed for 17 carcinomas with venous invasion compared with those without (median values 1·2 units *versus* 0·7 units respectively; $P < 0{\cdot}04$, *Figure 3*). Tissue plasminogen activator activity did not show any relationship to either of these parameters.

In eight patients who had undergone palliative resections the median tumour urokinase activity was also higher than in those patients who had undergone a curative resection (median values 1·6 units *versus* 0·8 units; $P < 0{\cdot}03$, *Figure 3*). Three of the four highest urokinase levels were from tumours associated with hepatic metastases. Again this parameter did not relate to tissue plasminogen activator activity.

There were 17 patients who had no evidence of disseminated disease, venous invasion or other than minimal local spread. This group consisted of four Dukes' stage A, ten stage B, and three stage C lesions each, however, with only one involved lymph node. This group of patients, considered to have a comparatively good prognosis, had tumour urokinase levels significantly lower than the remainder who comprised a poor prognosis group having one or more of the above parameters or more than four involved nodes (median values 0·6 units *versus* 1·0 units respectively, $P < 0{\cdot}03$, *Figure 3*).

Discussion

The present findings confirm both urokinase as a tumour associated antigen in colorectal cancer and our previously observed trend of increased biofunctional urokinase in adenomatous polyps. This latter finding accords with observations in experimental carcinogenesis where aberrant

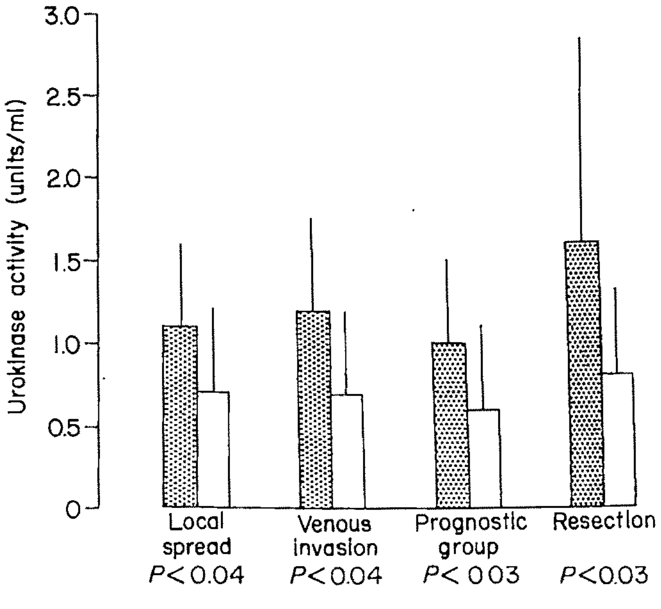

Figure 3 *Urokinase activity in colorectal carcinomas. Shaded areas compare these cases with moderate and extensive local spread, with venous invasion, the poor prognosis subgroup and those who had only a palliative resection with those who did not have these criteria. Urokinase activity is presented as median plus semi-interquartile range*

plasminogen activator activity, a feature typical of the malignant phenotype, is reported to precede the development of morphological features of malignancy[9].

There is little information relating to the physiological role of urokinase and, apart from its presence in kidney[10] and urine, its expression in other normal tissues appears to be minimal. In contrast tissue plasminogen activator is widely distributed in normal human tissues and is known to play a major physiological role in intravascular fibrinolysis. The present findings of comparatively high tissue plasminogen activator in normal colorectal mucosa and of elevated urokinase in carcinomas and adenomas have recently been corroborated by others[11,12].

Notwithstanding the problems of tumour heterogeneity and sampling as referred to previously[7], this study suggests that colorectal carcinomas with a poor prognosis are frequently associated with high urokinase activity whereas low levels of this protease are typical of tumours with a better prognosis. In the present study we were not able to demonstrate any relationship of urokinase activity to histopathological stage; however, Sim *et al.*[12] have recently reported a significant association between prourokinase activity and Dukes' staging and correlated activity with 'invasiveness'[12].

The prognostic significance in colorectal cancer of both the extent of local invasion[13,14] and the number of involved lymph nodes[13,15] in the resected specimen have been re-emphasized. The criterion employed to define the extent of local spread in this series was based on a previous study which demonstrated the worse prognosis associated with moderate and extensive local spread[16]. Recent data have demonstrated that by preliminary, multiple transverse full thickness sectioning of the gross specimen in rectal carcinoma, 27 per cent of cases that may not otherwise have been detected were found to have spread to the lateral resection margins[17]. In the present study eight cases did not undergo such sectioning in which local spread was assessed as <5 mm and it is, therefore, conceivable that, on the basis of the above data, local spread in a few of these may have been underestimated. Among those cases staged Dukes' C, there were three that had only a single involved lymph node and no evidence of either moderate or extensive local spread or venous invasion. These three patients were placed in the good prognosis group. It is noteworthy that this group of 17 patients with a good prognosis did have significantly lower urokinase levels.

Control mucosa was obtained from tumour-bearing specimens distant from carcinomas. We have previously investigated normal mucosa from non-neoplastic colons and, like others[18], found no difference in plasminogen activator activity from that in mucosa sampled distant from carcinomas in tumour-bearing specimens. Furthermore, in experimental rat colorectal neoplasia induced with dimethylhydrazine we have also demonstrated that, while abnormalities in plasminogen activator production are associated with both adenomas and carcinomas, in macroscopically normal mucosa, which could conceivably have undergone a field change, there is no such abnormality[19].

The anomalous expression of urokinase has been associated with various carcinomas, and has been implicated in tumour invasion and metastasis[19]. In addition to a fibrinolytic role, this enzyme, through the generation of plasmin, has been associated with the degradation of connective tissue proteoglycans, the degradation of the laminin and fibronectin components of basement membrane and with the activation of the collagenase enzyme system[20,21]. These biochemical processes are thought to play an important role in the mechanisms underlying local spread, venous invasion and dissemination of carcinomas and also the progression from adenoma to invasive carcinoma, where basement membrane destruction is an important event. It is, therefore, of interest that urokinase levels were higher in tumours with moderate or extensive local spread compared with those with minimal or without local spread and that the same pattern was observed for tumours with venous invasion. In a recent detailed study of peptidases in colorectal cancer[3], activity of cathepsin B, though not cathepsin D or collagenase, was found to be significantly higher in carcinomas that were invading locally and those with venous invasion. For these peptidases the ratios of median carcinoma to normal colonic wall activity ranged from 0·9 to 1·7 compared with ratios of urokinase activity of 4·5 for carcinoma:normal and 2·2 for polyp:normal. Activity of these peptidases however, was comparatively low in Dukes' D disease. This latter observation is in contrast with the present study in which high urokinase activity was noted when a palliative resection only was possible. Three of the four highest values were recorded in tumours associated with liver metastases. These observations are in keeping with the findings of Newstead *et al.*[22] who demonstrated increased fibrinolytic activity in primary colorectal cancers as well as in the tumour draining venous blood. In their study high tumour activity was particularly associated with carcinomas with a poor prognosis. Fibrinolytic activity in the tumour-draining venous blood correlated both with that in the primary tumour and with the recovery of circulating malignant cells suggesting that fibrinolytic enzymes were implicated in the shedding of tumour cells into the circulation.

It has been postulated that the deposition of fibrin on colorectal tumour cells which have invaded through a vein wall, possibly as a prelude to re-endothelialization is a defence mechanism[23]. Tumour cells with an enhanced capacity to produce urokinase and thus degrade this fibrin cap might, therefore, have a greater chance of escaping into the circulation and establishing a metastasis.

Urokinase has been associated with fetal cells[20] and its apparent association with certain poor prognostic features in colorectal cancer could be argued to be casual rather than causal, possibly reflecting the neo-expression of a fetal antigen. There is, however, experimental evidence also suggesting that this enzyme may contribute to tumour progression. Thus villous adenoma and colon carcinoma derived epithelial cells in culture have been demonstrated, when stimulated both by phorbol ester tumour promoters and by diglycerides endogenous to the large bowel to produce urokinase and production of this enzyme in an *in vitro* system coincided with invasive behaviour[24,25]. Additionally antibodies against this enzyme have been shown to inhibit experimental metastasis of a human tumour[26]. It may be argued that it is the balance between host defence mechanisms, such as lymphocytic infiltration, and the intrinsic biological properties of a tumour which confer 'aggressiveness' which determines outcome in an individual case. The above observations support the view that urokinase, probably via the local generation of plasmin within tumours, though possibly by some direct mechanism, may well contribute to this tumour 'aggressiveness' and thus progression of both colorectal carcinomas and premalignant adenomatous polyps.

This study has confirmed the increased expression of urokinase by colorectal carcinoma and suggests that this plasminogen activator may contribute to tumour progression. Further studies are indicated to evaluate the prognostic potential of this enzyme and whether manipulation of this enzyme system has a therapeutic role in the management of colorectal cancer.

Acknowledgements

Mr J. S. K. Gelister and Mr P. B. Boulos gratefully acknowledge support from Smith Kline and French Laboratories Ltd and from the Special Trustees of University College Hospital, London.

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Paper accepted 17 January 1987

Br. J. Surg. 1987, Vol. 74, June, 464

Technical modifications making on-table washout easier

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The value of on-table colonic lavage is well recognized and many surgeons now use it routinely in left colonic and restorative rectal resection. In the original technical description[1] the irrigant was introduced through a small ileotomy and evacuated above the lesion by intubating with anaesthetic scavenger hose through a transverse colotomy. In a later modification[2] the appendix stump was used safely instead of an ileotomy, and Paul's tubing on a flanged glass connector substituted for the more cumbersome anaesthetic hose.

Two further modifications have been found greatly to facilitate the manoeuvre. Firstly, instead of amputating the appendix and intubating its purse-stringed stump, the appendix is slit transversely and intubated like the cystic duct for cholangiography (*Figure 1*). Dealing with the stump afterwards is then much easier. Secondly, instead of intubating the colon above the lesion, which introduces the risk of contamination, the large bowel contents are evacuated rectally through a large cuffed endotracheal tube. The balloon is inflated and the effluent is diverted into a bucket resting on a stool placed between the patient's legs (*Figure 2*).

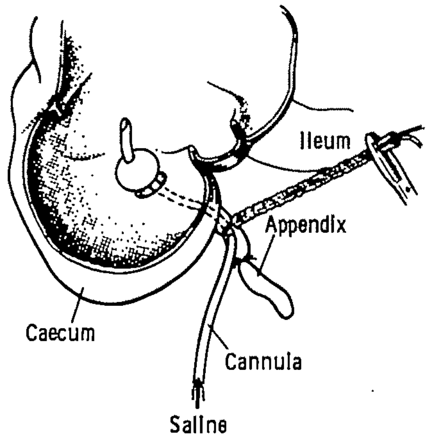

Figure 1 *The appendix is (dilated if necessary and then) intubated in a similar manner to the cystic duct for cholangiography*

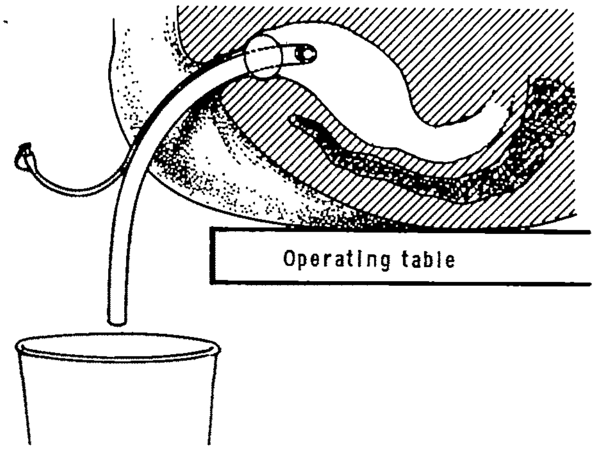

Figure 2 *The anal canal is intubated with a large endotracheal tube*

Before transection the bowel is cross-clamped, then irrigated or swabbed from below with cytotoxic or antiseptic solutions.

The manoeuvre has been found to be applicable in most cases, even, as is commonly the case, when the bowel is partially obstructed. Powerful purgation is routinely used on the pre-operative day to remove the bulk of faecal material. Even so a substantial quantity often remains when there is a degree of obstruction, which the method most satisfactorily clears.

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Paper accepted 17 February 1987

0007–1323/87/060464–01(1)$3.00

Br. J. Surg. 1987, Vol. 74, June, 464

Speeding up colonic lavage

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During the process of 'intra-operative colonic irrigation' in the management of left-sided large bowel emergencies as described by Dudley *et al.*[1], the bowel frequently intussuscepts down the rigid corrugated tubing: this delays the process and traumatizes the distal end of the colon.

By the simple insertion of a hypodermic needle into the plastic tubing air can pass into the tubing and prevent intussusception and the subsequent delay.

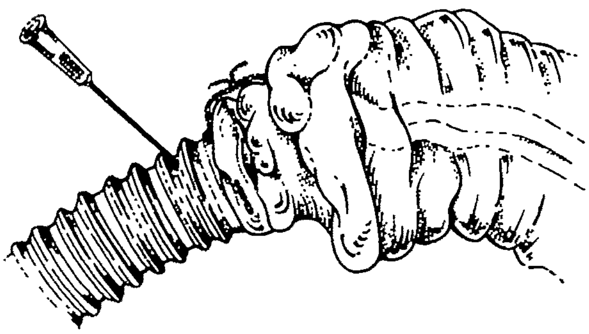

Figure 1 *Hypodermic needle allowing air to enter tubing*

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Paper accepted 7 January 1987

0007–1323/87/060464–01(2)$3.00

Br. J. Surg. 1987, Vol. 74, June, 465

Notes on 'on table' lavage

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Resection and primary colo-colic anastomosis for obstructing carcinoma of the colon is now an acceptable procedure since the introduction of colonic 'on table' lavage[1]. Its usefulness and efficacy have been demonstrated, and some modifications introduced[2]. The drawback of the technique lies in the use of some form of tubing to remove the lavage fluid and faecal debris. Prolonged lavage and manipulation is required to evacuate large boluses of constipated faeces—a serious disadvantage in elderly or frail patients. This problem is overcome by using a longitudinal colotomy of greater length than the diameter of the colon, through which even constipated faeces are readily evacuated. We report a modified technique with details of management which minimize wound and theatre contamination.

Technique

Requirements

The following are required:

1. A 24 FG Foley catheter plus intravenous giving set. A fine bore Foley catheter should be avoided—slow flow rates make it more difficult to flush out the colon.
2. Three 3 litre bags of normal saline warmed to 37°C. The last bag contained 1 g/l (i.e. 3 g) of tetracycline added just before infusion. 1·5 per cent glycine is not used because of its hypotonicity.

Procedure

The hepatic and splenic flexures are mobilized as part of the planned resection and to facilitate the flow of fluid and faeces. Gross gaseous distension can be relieved by suction aspiration through a 21 gauge needle inserted obliquely through a taenia of the transverse colon, as described by Lowdon[3].

By stab incision the Foley catheter is brought through the abdominal wall at a site appropriate to a tube caecostomy and is placed through the appendicular stump or, if there is no appendix, through the anterior wall of the caecum (preferably through one of the taenia). In each case it is inserted through a stab incision within a 000 catgut purse string suture. At the end of the lavage, the catheter should be converted into a caecostomy with one or two further purse string sutures and four sutures between the caecum and the parietal peritoneum of the anterior abdominal wall, around the emerging catheter. The left colon and its mesentery are mobilized as for resection and the bowel is divided between clamps at its distal anastomosis site. The site of proximal bowel division is dissected and cleared but bowel clamps should not be applied at this stage. If necessary, the resected mesentery is divided further until the site of obstruction can be delivered outside the abdomen into a receptacle held at the side of the operating table. A clamp is applied just proximal to the site of obstruction and, as the bowel is delivered into a bowl or plastic bag, a longitudinal antimesenteric colotomy is made, greater than the diameter of the colon, proximal to the clamp (*Figure 1*).

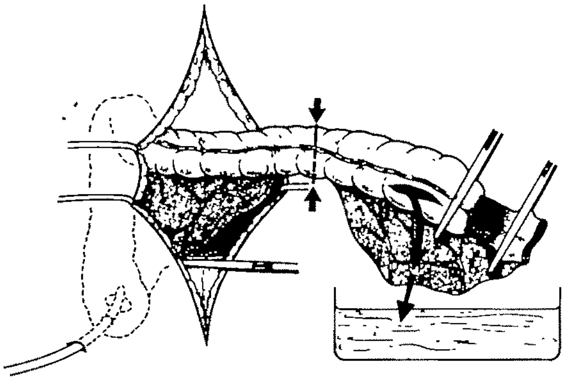

Figure 1 *A diagram depicting the described technique in a patient with a carcinoma involving the sigmoid colon.* ↕ *Site of anastomosis prepared for clamping and division at conclusion of lavage*

Lavage is carried out into a large bowl or into a VI-Drape 45 × 45 cm isolation bag with the tapes tied proximally around the specimen if the effluent is excessively offensive. The lavage is continued until the effluent is clear and the infusion bag is lowered to allow any residual irrigation to drain back. The bowel to be retained remains within the operative field throughout the procedure; only the bowel to be resected lies outside the abdomen.

Two Payr's clamps are applied at the site of the proximal resection and the bowel is divided between them to allow the whole specimen to drop into the bowl. The surgeon may then proceed to anastomosis. An intravenous infusion of 1–2 mg glucagon may be useful if the left colon goes into marked spasm, usually seen in severe diverticular disease and exacerbated by lavage with inadequately warmed fluid.

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Paper accepted 24 January 1987

0007–1323/87/060465–01$3.00

Br. J. Surg. 1987, Vol. 74, June,
466–468

Mammillary fistula

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Forty women presenting with mammillary fistulas over a 6 year period have been reviewed. The events preceding the fistula were incision of a periareolar breast abscess (n = *24*)*, breast biopsy* (n = *13*) *and spontaneous discharge of an inflammatory mass* (n = *3*)*. Only two of the women with abscesses were lactating. Two patients had granulomatous mastitis. The remaining 36 patients were all considered to have periductal mastitis/mammary duct ectasia as the cause of their fistulas. The two mammillary fistulas associated with lactation healed spontaneously. Nine patients had the fistula excised and the wound packed; this resulted in satisfactory healing in all but one patient. Twenty-one patients had excision of the fistula and primary closure, without antibiotic cover, but only ten healed without complications and six patients required further surgical procedures for a recurrent fistula. Six patients had primary excision and closure under antibiotic cover with a penicillin and metronidazole; all healed. Mammillary fistulas are complications of the periductal mastitis/duct ectasia syndrome. They should be treated by excision and primary closure under appropriate antibiotic cover or alternatively excised and left open to granulate.*

Keywords: Mammillary fistula, duct ectasia, periductal mastitis

The term mammillary fistula was first introduced by Atkins in 1955[1] to describe the fistulas of the lactiferous ducts which had been reported by Zuska *et al.* in 1951[2]. The aetiology of this condition is still not clear. In early reports it was suggested that it was due to duct obstruction[1], possibly predisposed by a congenital abnormality of the ducts which were lined with squamous epithelium[3]. However, its association with juxta-areolar abscess and duct ectasia was subsequently recognized, and stressed, by Sandison and Walker[4]. The preferred method of surgical treatment of mammillary fistula is uncertain. Some advocate excision of the fistula, its related lactiferous duct and surrounding fibrosis; others, particularly Atkins, opened up and saucerized the fistula and duct, by cutting down on a probe passed through the fistula and involved duct, and allowed the wound to granulate. All authors stress the importance of removing or marsupializing the originating duct.

The aim of this study was to investigate the aetiology of this condition and to assess the results of different surgical procedures by reviewing experience with mammillary fistulas over a 5-year period in two Edinburgh hospitals.

Patients and methods

A retrospective study of 40 patients with mammillary fistulas treated in the Royal Infirmary of Edinburgh and in the Longmore Breast Unit between 1978 and 1983 has been undertaken. The notes of all these patients have been reviewed and full clinical and operative details extracted. Follow-up information from 1–7 years was available for all patients. The histology of the fistulas and that of all previous biopsies was also reviewed from pathology records and in some cases by further study of the tissue. No bacteriology was included in this study, as it was not available in the majority of cases reviewed.

Clinical features

The age range of the patients in this series was from 24 to 61 years with a median of 35 years. The time the patients had the fistula before surgery varied from 1 month to 4 years; 11 patients had their fistula for longer than 1 year.

One of three events immediately preceded the fistula. These were:

(i) incision and drainage of an abscess (24 patients),
(ii) breast biopsy (13 patients),
(iii) spontaneous discharge of an inflammatory mass (3 patients).

Two of the twenty-four patients who had an abscess incised and drained immediately before the fistula developed were lactating at the time their abscess developed. The remaining 22 were not, the inflammation having no apparent preceding cause. In 23 patients the nipple of the affected breast was noted to be inverted at the time the fistula was treated. Eleven complained of a nipple discharge.

Thirty-three patients had a history of breast disease which had preceded, by some time, the event which led to the fistula. Nineteen of these thirty-three patients had a total of thirty-five non-lactating breast abscesses incised and drained, twelve had undergone a total of eighteen breast biopsies and two patients had contralateral mammillary fistulas successfully treated. A further two patients developed a contralateral mammillary fistula after the study period, i.e. during subsequent follow-up. Four patients, therefore, had bilateral fistulas.

Mammograms were performed in 19 patients and were reported as showing radiographic evidence of duct ectasia in 8. This consisted of prominent ducts, periductal opacification and coarse linear and irregular calcification.

Treatment

The treatment for mammillary fistulas varied according to the unit on which the patient was treated and the time during the period under review.

In two patients whose fistulas followed drainage of a lactational abscess, a course of flucloxacillin healed the fistula. Two further patients whose fistulas were not associated with lactation had resolution following a 1 week course of flucloxacillin and metronidazole. The remaining 36 patients were treated surgically.

The surgical procedure described in the operation notes suggested that in all cases the fistula and its related duct were identified, by insertion of a probe through the fistula to emerge at the nipple, and were excised. The resulting wound was either (a) left open and packed with eusol (9 patients) then being either allowed to heal spontaneously (3) or have a delayed primary closure (6); or (b) primarily closed either without (21 patients) or with (6 patients) antibiotic cover with flucloxacillin 500 mg four times daily and metronidazole 400 mg three times daily. These antibiotics were started pre-operatively and continued for at least 5 days. Those patients who had a delayed primary closure were treated in the Longmore Breast Unit, a subcuticular suture being inserted at the

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0007–1323/87/060466–03$3.00

time of excision and pulled tight in 3–5 days when the wound appeared clean. Similarly the patients receiving flucloxacillin and metronidazole were treated in our Breast Unit, this combination of antibiotics being appropriate to the organisms which we have recently shown to be present in mammillary fistula[5].

The operation wound of all 36 patients have been reviewed until healed. Wound infections (discharge of pus), prolonged wound discharge (discharge from the wound present 1 month after surgery) or recurrence of mammillary fistulas were noted. Comparison of the frequency of these problems in the three treatment groups was compared by Fisher's exact test.

Results

The results of these three methods are shown in *Table 1*. Eight of nine wounds which were packed, including all in the six patients having a delayed primary closure, healed. Less than half of the wounds treated by immediate primary closure healed without further problems but all six treated by immediate primary closure under antibiotic cover did heal.The success rates of packing the wound or closure under antibiotic cover were significantly better than primary closure alone ($P = 0{\cdot}036$ and $P = 0{\cdot}027$ respectively).

Five patients whose fistulas were treated by primary closure alone and one whose wound was packed developed a recurrent fistula. They underwent a total of seven further operations. Two patients had the fistula excised and left open to granulate and one had total excision of the subareolar duct system. All three healed. The other three patients had a further excision and primary closure without antibiotic cover; two failed to heal again and one patient underwent a further excision under antibiotic cover with successful healing. One patient refused further surgery and still has her fistula.

Histology

As previously indicated two patients were lactating at the time their fistula developed. Two patients had granulomatous mastitis. All of the remaining 36 patients, on review of previous and current breast biopsies and fistula specimens, had histological evidence of periductal mastitis/duct ectasia[6].

In 25 patients periductal inflammation was present without signs of duct dilatation or true duct ectasia. The periductal inflammatory infiltrate consisted of polymorphs, occasional granulomas and chronic inflammatory cells in 10; and chronic inflammatory cells only (plasma cell mastitis) in 15. Eleven patients had duct dilatation (duct ectasia) associated with a chronic periductal inflammatory reaction. All these biopsies therefore come within the spectrum of periductal mastitis/duct ectasia syndrome we have previously described[6].

Discussion

We have previously shown that a range of pathological changes occur in the clinical syndrome of duct ectasia, varying from the earliest changes of periductal inflammation without duct dilatation to duct dilatation with little surrounding inflammatory reaction. An identical range of changes was seen in the majority of patients with mammillary fistulas in this series. As indicated above, the factors which are regarded as being concerned in the aetiology of mammillary fistula include duct obstruction[1], congenital squamous lined ducts[3] and duct ectasia[4,7]. Our retrospective review of 40 patients with mammillary fistulas suggests that periductal mastitis/duct ectasia is the most significant underlying pathological cause. Thus, 27 patients had known inflammatory complications of this syndrome while 13 had a previous breast biopsy; all but 4 (2 of whose fistulas were associated with lactation) had histological evidence of periductal inflammation. The other 2 showed granulomatous mastitis which, although now recognized as a distinct entity[8], may also be a variation of the periductal mastitis/duct ectasia syndrome.

Sixty per cent of the women in this series also had indrawn nipples, a known feature of periductal mastitis/duct ectasia. Atkins first suggested that nipple inversion might have a causal relationship but cause and effect are difficult to separate, particularly as nipple retraction is a common sign of the early stages of this disease[1]. We have no information on the time relationship of nipple inversion in the case studied and no particular action to correct this was apparently taken.

Although earlier studies suggested that the inflammatory lesions associated with periductal mastitis/duct ectasia (peri-areolar inflammatory mass) and juxta-areolar abscess were sterile, anaerobic organisms have subsequently been isolated from these lesions[9,10]. Recently, we have demonstrated that if appropriate transport and culture methods are used both aerobic and anaerobic organisms can be isolated from nipple discharge associated with duct ectasia. In addition we found a similar range of organisms to be present in the discharge from mammillary fistulas[5], providing further evidence of their relationship to the periductal mastitis/duct ectasia syndrome.

In view of the presence of organisms in mammillary fistulas it is not surprising that the results of surgical excision and primary closure are not good, only 50 per cent healing satisfactorily. Excision and packing were generally successful. Allowing the wound to granulate was advised by Atkins[1] but this procedure does require some 6 weeks of regular supervision of the wound (Atkins advised 4 hourly dressings for 3 weeks). In our experience this can safely be shortened by delayed primary closure.

Although the numbers are small it would also appear that the addition of appropriate antibiotic therapy may allow immediate primary closure to be successfully performed but further experience of the effect of antibiotic cover is required.

The treatment of *recurrent* mammillary fistulas is difficult and has included major duct excision and even mastectomy[11,12]. Further excision, leaving the wound open to granulate or primary closure with long courses of antibiotics has usually proved successful in our experience. As a result of this review, we would stress that, even after excision of the fistula and underlying duct system, primary closure of these lesions without antibiotic therapy is inappropriate; the wound should be packed and left open or closed as a delayed procedure. Primary closure under appropriate antibiotic cover may be preferable but requires further study.

Acknowledgements

We are grateful to Dr T. Anderson and the staff of the Department of Pathology, University of Edinburgh, for their help in reviewing the pathological findings and to the consultant surgeons of the Royal Infirmary for allowing us to study records of their patients.

Table 1 *Outcome of treatment in patients undergoing surgery for mammillary fistula*

	Number of patients	Number healing successfully	Number with prolonged wound discharge	Number with recurrent fistula
Excision and packing	9	8	1	1
Primary closure alone	21	10	6	5
Primary closure under antibiotic cover	6	6	0	0

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Paper accepted 16 December 1986

Case report

Br. J. Surg. 1987, Vol. 74, June, 468

Mondor's disease in the groin

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Mondor's disease, which has only recently been described in Nigerians, is in fact not rare in negro Africans[1]. The disease is not confined to the breast and contiguous thoraco-abdominal wall. It has been described in the antecubical fossa[2]. This paper describes the first case of Mondor's disease in the groin.

Case report

A 10-year-old boy presented with a 3 week history of a painful swelling in the right groin. He denied any history of trauma. The mass appeared spontaneously. On examination a vertical cordlike, tender lump running superiorly from the inguinal ligament towards the umbilicus was found (*Figure 1*). The mass which was intradermal did not give a positive cough impulse and could not be reduced. There was no evidence of systemic disease. An impression of thrombophlebitis of the right superficial epigastric vein was made. An excision biopsy was performed in order to exclude a parasitic cyst.

At operation an irregular, beaded, enlarged, chronically inflamed mass measuring 6 × 0·8 cm was excised. Histology revealed organized blood clot occluding the lumen of a destroyed, fibrotic and chronically inflamed segment of vein.

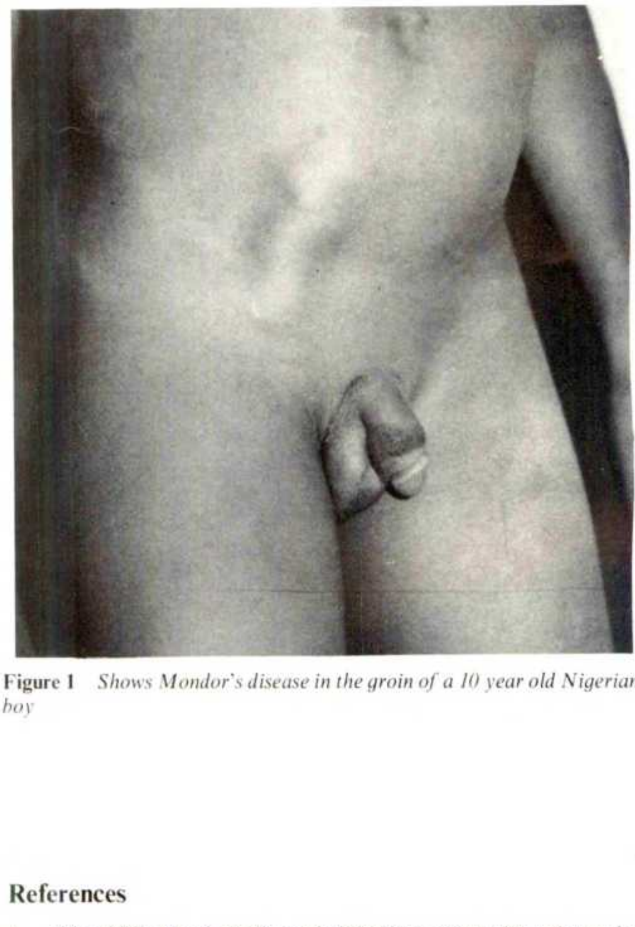

Figure 1 *Shows Mondor's disease in the groin of a 10 year old Nigerian boy*

Discussion

Henri Mondor's original description of this disease was in relation to the breast and thoraco-abdominal wall. However the disease is now known to occur at other sites[2]. Since infection and trauma[3] and recently filariasis[4] have been incriminated as possible aetiological agents, it is not surprising to find the occurrence of Mondor's disease in the groin especially of an African child prone to trauma, infection and filarial infestation. This is the first description of Mondor's disease in the groin and in a child.

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Paper accepted 2 February 1987

Br. J. Surg. 1987, Vol. 74, June, 469–470

Review of a hospital experience of breast abscesses

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A retrospective review of breast abscesses during a 10-year period was performed. Only 8·5 per cent (6/72) of patients were in the puerperium. Peripherally sited abscesses were predominantly staphylococcal in origin, incision and drainage was effective treatment in all. By contrast, a subareolar abscess yielded a higher proportion of anaerobic bacteria and 46 per cent (13/28) of these patients had duct ectasia. We conclude that in present day practice a breast abscess is more likely to be related to duct ectasia than to the puerperium, and that patients with anaerobic infection or subareolar abscesses should be assumed to have duct ectasia and may require excision of the major duct system (Hadfield's procedure).

Keywords: Breast abscess, mammary duct ectasia

In modern practice breast infection is treated with antibiotics. The incidence of breast abscess is said to be declining[1] and we felt that this had led to a change in the type of disease being seen in hospital today. Since the description of mammary duct ectasia as a pathological entity[2] clinicians have increasingly recognized that many episodes of subareolar infection are caused by these changes in the duct system. Therefore, we undertook a retrospective review of the records of all women presenting with a breast abscess during the past 10 years.

Methods

The case notes of all women presenting to the Northern General Hospital who had been diagnosed as having a breast abscess in the previous 10 years were reviewed (1 January 1976 to 31 December 1985). Breast abscess was defined as an acute inflammatory lump which yielded pus on incision. The site of the breast abscess was classified as subareolar (arising within 1 cm of the areola), peripheral (arising more than 1 cm away from the areola), or indeterminate (where the abscess extended over both sites and its origin in relation to the nipple could not be determined). Details were recorded of clinical features, antibiotics employed, bacteriology and subsequent outcome.

Results

Seventy-two patients presented with a breast abscess in the 10-year period. Several patients had experienced more than one episode of abscess formation, but for the purpose of this study only the first presentation was considered. Only 8·5 per cent (6/72) of patients were in the puerperium and only 3 per cent (2/72) of these were lactating at the time of presentation. *Table 1* shows the results of the bacteriology related to the site of the abscess, either subareolar, peripheral or indeterminate. The subareolar abscesses were most commonly infected with anaerobic bacteria.

Of the women who had abscesses which grew anaerobic organisms 90 per cent (9/10) had subsequent inflammatory episodes of the same breast. Three of the ten patients had more than five abscesses drained in more than a 3-year period and all had a subsequent curative duct excision. Of the remaining seven patients, five had a prolonged recovery with persistent discharge lasting more than a month or had mamillary fistulae which, when excised, showed histological evidence of duct ectasia (3/10).

The site of the abscess was a useful predictor of subsequent outcome (*Table 2*). Twenty-one patients (75 per cent) with a subareolar abscess had a complicated recovery. This ranged from a persistent lump at the site of the abscess to persistent discharge from the nipple or a mamillary fistula (32 per cent—9/28). Of patients presenting with a subareolar abscess, 21 per cent (6/28) went on to a Hadfield's procedure[3]. Review of histology from all patients who had a complicated subareolar abscess or an anaerobic abscess (13) showed the features of mammary duct ectasia as described by Azzopardi[2].

Most peripheral and indeterminate abscesses grew *Staphylococcus aureus*, *S. albus* or a streptococcus (68 per cent – 30/44). All the peripheral abscesses occurred in premenopausal women and all had an uncomplicated recovery following incision and drainage or, in three cases, incision and primary sturue.

Antibiotic treatment was also studied. We found that those patients who had been prescribed antibiotics had received a wide range of different preparations (*Table 3*). The commonest drugs were flucloxacillin and ampicillin (10 patients each) and only three patients had received metronidazole.

Discussion

Our findings agree with those of Benson and Leach *et al.*[4,5] that the incidence of puerperal breast abscess and of breast abscesses in general is much less frequent than in previous decades. These figures show that few are related to the puerperium. This suggests that peripheral breast abscesses are much the same as subcutaneous abscesses elsewhere[6]. They are usually caused by *S. aureus*, require incision and drainage and almost always have an uncomplicated recovery. Puerperal breast abscesses tend to be peripheral and to fall into this category.

Table 1 *Distribution of organisms* versus *abscess site in the 72 patients (subareolar = within 1 cm of the areola; peripheral = more than 1 cm away from the areola and indeterminant when too large to differentiate into either of the two other groups)*

	S. aureus	Bacteroides	No growth	Total
Subareolar	5	8	15	28
Peripheral	22	1	10	33
Indeterminate	8	1	2	11

Table 2 *Number of patients experiencing problems postoperatively in that they needed more than one out-patient visit or further surgery*

	S. aureus	Bacteroides	No growth	Total
Subareolar	1	7 (f = 3)	13 (f = 6)	21
Peripheral	1	1	1	3
Indeterminate	0	1	1	2

f, Mamillary fistula

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Table 3 *Antibiotics used in breast sepsis*

	S. aureus	Bacteroides	No growth
Erythromycin	2		
Ampicillin	5		5
Flucloxacillin	6	2	2
Metronidazole	2		1
Cephalexin			1
Penicillin V	3		3
Trimethoprim	1		
Clindamycin		1	
Total	19	3	12

In contrast 75 per cent (21/28) of patients with subareolar abscesses developed further problems, despite adequate incision and drainage, a somewhat higher figure than the 39 per cent found by Ekland[7]. This high incidence of problems following incision and drainage of subareolar abscess, though noted more than 10 years ago[5,7], does not appear to be widely recognized. Excision of the major duct system[3] was completely effective in eradicating recurrent problems in these women.

Haagensen[8] described what he called mammary duct ectasia in 1951 as an inflammatory disease of the major duct system deep to the nipple and areolar. Histologically there is a periductal inflammation around dilated ducts which may contain cellular debris and lipid rich material[2,8]. In the commoner chronic form this inflammation may lead eventually to fibrosis and atrophy of the duct system. Duct ectasia, however, may present acutely as an abscess[2] often caused by an anaerobic organism[9]. It has been stressed that effective treatment is to remove the underlying cause by excision of the major duct system[3,9].

A recent paper by Lambert *et al.*[10] examined mamillary fistula as a clinical problem. Although we agree that 'mamillary fistulae should be suspected and sought in all patients presenting with abscesses adjacent to the nipple' we dispute their suggestion that these fistulae are not a part of duct ectasia. All such fistulae in our series showed evidence of chronic inflammation, debris and dilated ducts, satisfying Azzopardi's pathological definition of duct ectasia[2]. Lambert *et al.*[10] have reported good results from excision and saucerization of fistulae, but if duct ectasia is indeed the basic pathology then excision of the duct system would seem more logical; as originally suggested by Patey and Thackray[11].

The relatively high proportion of swabs yielding no growth may reflect antibiotic treatment before admission, but also may be due to the difficulty in transporting and culturing anaerobic organisms. Bundred *et al.*[12] found that by using appropriate transport media they could culture both aerobic and anaerobic organisms from the lesions of mammary duct ectasia in a high proportion of patients and from all patients with periareolar sepsis.

Antibiotic treatment for breast sepsis is controversial. Our patients had received numerous different antibiotics some of which were inappropriate given the likely organisms. We feel it is reasonable to assume in women not in the puerperium that the organism is either *Staphylococcus* or an anaerobe and, therefore, either a combination of flucloxacillin and metronidazole or amoxycillin and clavulanic acid (Augmentin) as a single agent would be appropriate antibiotics. Benson[4] claims that the institution of appropriate chemotherapy in the early stages of sepsis is warranted as small amounts of pus are impossible to detect clinically and that many episodes settle without surgery. This point is also confirmed by Bates' questionnaire[1] about the treatment of breast sepsis suggesting that a large number of patients with breast sepsis are treated satisfactorily in the community.

Haagensen[8] suggests that treatment of episodes of inflammation, which occur repeatedly as part of the disease process of duct ectasia, can be avoided by timely use of appropriate antibiotics. None of our 13 patients with proven duct ectasia had received appropriate antibiotics.

We conclude that any woman presenting with a subareolar breast abscess caused by an anaerobic organism probably has duct ectasia and should be treated accordingly. On the other hand peripheral abscesses appear to behave as subcutaneous abscesses elsewhere in the body are are satisfactorily treated by incision and drainage.

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471–473

Evaluation of hepatic resection for hepatocellular carcinoma in the elderly

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The results of 139 hepatic resections in 154 patients with hepatocellular carcinoma (HCC) operated upon in the last 6 years are reported. These 139 Japanese patients were classified into three groups according to age. Group I included 58 patients under 55 years of age, group II 44 aged from 56 to 65 years and group III 37 aged over 66 years. Fewer cases in group III had histological evidence of cirrhosis than in the other two groups. There was a statistically significant marked decline in the pre-operative cardiac and pulmonary function in group III patients. However, there was no statistical difference in postoperative complications, mortality and survival rate among the three groups. The results after hepatic resection seemed to depend on pre-operative liver function and histology, and on control of the haemorrhage at operation. The results indicate that liver surgery for elderly patients with hepatocellular carcinoma is justifiable given careful patient selection.

Keywords: Hepatocellular carcinoma, geriatric surgery, postoperative complications

Recently, the development of liver surgery has resulted in the safer treatment of hepatocellular carcinoma (HCC)[1–3]. On the other hand, the increase of life span which has resulted from advances in medical care and the development of diagnostic procedures for HCC have increased the incidence of HCC detected in elderly patients. Although there are some therapeutic alternatives, surgery by hepatectomy remains essentially the method of choice. It is our policy that HCC should be operated on wherever possible, even in elderly patients. Hence, the question arises whether surgery in the elderly leads to an increase in operative mortality and postoperative complication rates. There are some reports of surgery in the geriatric age group[4–8], but there are few reports on liver surgery in elderly patients.

This report concerns an assessment of pre-operative findings, postoperative complications, mortality and the results of surgery for HCC undertaken in elderly as opposed to younger patients in the period 1980–1986.

Patients and methods

One hundred and fifty-four Japanese patients with HCC, with no other malignancies, were electively operated on in our department between October 1979 and February 1986. Twenty-four underwent cannulation of the hepatic artery without hepatic resection because of severe liver dysfunction or huge HCC. Thus, 130 of these patients underwent hepatic resection between January 1980 and February 1986. Nine had second hepatectomy operations due to recurrence[9]. Thus, the total number of hepatectomy operations was 139. These 139 patient operations were classified into the following three groups according to age (*Table 1*). Group I was composed of 58 patients under 55 years of age, group II of 44 aged from 56 to 65 years and group III of 37 aged over 66 years. After pre-operative examination of pulmonary, cardiac, hepatic and renal function, hepatectomy was performed.

Criteria of abnormality in pre-operative investigation were as follows: lung: percentage with vital capacity (VC) <60 per cent and/or FEV1·0 per cent <70 per cent (FEV1·0 per cent is the ratio between 1 second forced expiratory volume/forced vital capacity; normal values: percentage VC ≥ 80 per cent, FEV1·0 per cent ≥ 70 per cent); heart: abnormal ECG; kidney: phenolsulphonphthalein (PSP) $15' < 20$ per cent and $120' \leq 60$ per cent (normal value: PSP $15' \geq 25$ per cent or PSP $120' \geq 70$ per cent). Liver function was assessed by Child's classification[10] and indocyanine green (ICG) retention tests (ICG R15′: normal value 0–10 per cent). Tests were also made for diabetes mellitus and hepatic cirrhosis. Diabetes was diagnosed by glucose tolerance test. Liver cirrhosis was diagnosed histologically.

Postoperative complications were carefully monitored. Operative death means that the patient died within 30 days after the operation. Curative operation meant that the patient appeared to be completely cancer-free at the end of the operation or after diagnostic testing at the time of discharge. Survival was analysed by Kaplan and Meier's actuarial method[11]. The statistical analysis of survival rates was made using the generalized Wilcoxon test[12] and other statistical analysis was performed using χ^2 analysis with Yates' correction factor[13]. A value of $P<0.05$ was considered to be statistically significant.

Results

Concomitant disease

All the patients were examined for the presence of hepatic cirrhosis and diabetes mellitus. The number of cirrhotic cases was 52 (90 per cent) and 41 (93 per cent) in groups I and II, whereas it was 25 (68 per cent) in group III. There is a statistically significant difference between groups I and II, and group III ($P<0.01$). The number of diabetic cases was 19 (33 per cent), 7 (16 per cent) and 6 (16 per cent) in groups I, II and III, respectively. There is no statistically significant difference between them.

Pre-operative examination

PSP: abnormal PSP was detected in 1 (2 per cent) patient in group I, 5 (11 per cent) in group II and 5 (14 per cent) in group III (*Table 2*). There is no statistically significant difference among the three groups.

ECG: the ECG was abnormal in two patients (3 per cent) in group I, five (11 per cent) in group II and ten (27 per cent) in group III (*Table 2*). There is a statistically significant difference between groups I and III ($P<0.01$).

Table 1 *Details on patients undergoing hepatic resection for HCC*

	Group I	Group II	Group III	Total
No. of cases	58	44	37	139
Age (years)				
Range	17–55	56–65	66–78	17–78
Mean	48·7	60·5	70·1	58·1
Sex (*n*)				
Male	50	39	30	119
Female	8	5	7	20

Table 2 *Pre-operative examination of patients undergoing hepatic resection*

	Group I ($n=58$)	Group II ($n=44$)	Group III ($n=37$)	Total ($n=139$)
Abnormal PSP				
Yes	1	5	5	11
No	56	37	31	124
Unknown	1	2	1	4
Abnormal ECG				
Yes	2^{a}	5	10^{a}	17
No	54 } 56^{a}	37	26 } 27^{a}	117
Unknown	2	2	1	5
Abnormal spirogram				
Yes	3^{b}	8	11^{b}	22
No	54 } 55^{b}	34	25 } 26^{b}	113
Unknown	1	2	1	4

a, $P<0\cdot01$; *b*, $P<0\cdot01$

Table 3 *Pre-operative liver function in patients undergoing hepatic resection*

	Group I ($n=58$)	Group II ($n=44$)	Group III ($n=37$)	Total ($n=139$)
Child's grade				
A	49	27	28	104
B	8	15	8	31
C	1	2	1	4
ICG R15′				
$\geq 20\%$	30	25	18	73
$<20\%$	27	18	19	64
Unknown	1	1	0	2

Spirogram: the spirogram results were abnormal in three patients (5 per cent) in group I, eight (18 per cent) in group II and 11 (30 per cent) in group III (*Table 2*). There is a statistically significant difference between groups I and III ($P<0\cdot01$).

Liver function: The number of Child's C patients was 1 (2 per cent) in group I, 2 (5 per cent) in group II and 1 (3 per cent) in group III. The majority of cases were classified into Child A and B (*Table 3*). The results for ICG R15′ revealed the number of cases with impairment of over 20 per cent to be 30 (52 per cent) in group I, 25 (57 per cent) in group II and 18 (49 per cent) in group III, respectively (*Table 3*). There is no statistically significant difference between the groups in either Child's classification or ICG R15′.

Operation

In group I, 51 cases had hepatectomy of one segment or less. Six of these had simultaneous operation for oesophageal varices in the form of a distal splenorenal shunt (DSRS). Two cases underwent lobectomy, five cases trisegmentectomy. In group II, 38 cases had hepatectomy of one segment or less. Three had a simultaneous DSRS and two had partial colectomy for direct cancer invasion. Three cases underwent lobectomy and three cases trisegmentectomy. One of the lobectomized cases and one of the trisegmentectomized cases underwent portal thrombectomy. In group III, 27 cases had hepatectomy of one segment or less, one of whom had a simultaneous DSRS. Two cases underwent hepatectomy of less than one lobe. Five cases underwent lobectomy. One had a simultaneous reconstruction of the biliary tract, and one underwent partial resection of the diaphragm.

Intra-operative blood loss

Blood loss exceeding 3000 ml was seen in 14 patients (24 per cent) in group I, 5 (11 per cent) in group II and 7 (19 per cent) in group III, respectively. No statistically significant difference was noted.

Postoperative complications

Table 4 lists the complications that arose after hepatectomy in each group. Postoperative complications occurred in 15 (26 per cent) patients in group I, 15 (34 per cent) in group II and 9 (24 per cent) in group III. No statistical difference was seen between the three groups. In each group, the leading complications were hepatic failure, gastrointestinal bleeding, intraperitoneal bleeding and bile leakage.

Mortality

There were five (11 per cent) operative deaths in group II, whereas there were two (3 per cent) and two (5 per cent) in groups I and III respectively. No statistically significant difference was seen among the groups. In group I, one patient died of variceal bleeding, another of coagulopathy. In group II, three died of hepatic failure and one underwent extended right lobectomy. One died of coagulopathy and one died of hepatic failure following postoperative intraperitoneal bleeding. In group III, one patient died of pneumonia and another of hepatic failure following extended right lobectomy with massive bleeding. All of these deaths were associated with liver cirrhosis except for one patient in group III.

Long-term results

The Kaplan–Meier life table estimate of cumulative survival at 1, 3 and 5 years for those who underwent hepatic resection in group I was 82·8 per cent, 49·0 per cent and 36·8 per cent, respectively. In group II, it was 77·3 per cent, 41·5 per cent and 27·7 per cent. In group III, it was 81·1 per cent, 45·2 per cent and 18·1 per cent (*Table 5*). The survival rates of curatively resected cases are shown in *Table 6*. There was no statistically significant difference in the survival rates among the three groups as shown in *Tables 5* and *6*, although only a small proportion of our patients are eligible for 5-year assessment.

Discussion

In the present study, there is a statistically marked decline in the pre-operative cardiac and pulmonary function of the elderly patients. On the other hand, no significant difference was seen in hepatic and renal function between the three groups. Fewer patients had histologically proven cirrhosis in group III than in the other two groups. This seems to influence the results after hepatectomy much more than pre-operative cardiac and

Table 4 *Postoperative complications in patients undergoing hepatic resection*

	Group I	Group II	Group III
Gastrointestinal bleeding	6 (4)		1 (1)
Variceal bleeding	1 (1)		
Postoperative intraperitoneal bleeding		3 (2)	2 (2)
Hepatic failure	2 (2)	5 (5)	1 (1)
Bile leakage	2 (2)	1 (1)	1 (1)
Coagulopathy	1 (1)	1 (1)	
Intractable ascites	2 (2)		
Pleural effusion	1 (1)		2 (1)
Acute respiratory distress syndrome		1 (1)	
Atelectasis		1 (1)	
Pneumonia			1 (0)
Abdominal pain (neuralgia)		1 (1)	
Leakage of colonic anastomosis		2 (2)	
Superior mesenteric artery occlusion			1 (0)
Total	15 (13)	15 (14)	9 (6)

Numbers in parentheses are number of cases with associated cirrhosis

Table 5 *Survival of patients after 139 hepatectomy operations*

Group	No. of patients	1 year		2 years		3 years		4 years		5 years	
		Number*	%	Number	%	Number	%	Number	%	Number	%
I	58	48/58	82·8	36/45	66·2	20/27	49·0	9/12	36·8	3/3	36·8
II	44	34/44	77·3	20/31	49·9	10/12	41·5	4/4	41·5	2/3	27·7
III	37	30/37	81·1	25/29	69·9	11/17	45·2	2/5	18·1	1/1	18·1

* Absolute number of patients surviving/number eligible for each year analysis
Group I *versus* II: $z=1{\cdot}240$: II *versus* III: $z=1{\cdot}135$; III *versus* I: $z=0{\cdot}085$. There is no statistical difference among the three groups

Table 6 *Survival rate of curatively resected cases*

Group	No. of patients	1 year		2 years		3 years		4 years		5 years	
		Number*	%	Number	%	Number	%	Number	%	Number	%
I	44	41/44	93·2	33/38	80·9	18/24	60·7	8/11	44·1	3/3	44·1
II	37	31/37	83·8	20/28	59·8	10/12	49·9	4/4	49·9	2/3	33·2
III	33	27/33	81·8	24/26	75·5	10/16	47·2	2/5	18·9	1/1	18·9

* Absolute number of patients surviving/number eligible for each year analysis
Group I *versus* II: $z=1{\cdot}735$ ($P<0{\cdot}10$); II *versus* III: $z=0{\cdot}551$; III *versus* I: $z=1{\cdot}204$. There is no statistical difference among the three groups

pulmonary function. Indeed, all operative deaths, except one, were associated with liver cirrhosis. Moreover, the major causes of postoperative death were liver dysfunction and massive bleeding. These results suggest that the outcome of hepatic surgery depends more on two specific factors than on pre-operative examination of organ function. One is liver dysfunction, especially in the presence of histological cirrhosis; the other is control of haemorrhage. This may explain why there is no difference in the results after hepatectomy among the three groups, in spite of more pre-operative cardiac and pulmonary dysfunction in the elderly. Fewer cases were complicated with histological cirrhosis in the elderly. However, it is conceivable that there might be better monitoring of postoperative elderly patients in our hospital.

The relative infrequency of histological cirrhosis in our elderly patients is of interest. One explanation may be that liver cirrhosis is usually seen in middle age and its prognosis is poor[4,15], whereas HCC is thought to be a terminal form of hepatic cirrhosis. Thus, inevitably, there might be fewer cases of HCC with liver cirrhosis in the elderly.

Although alternative treatments for HCC are reported, only surgical treatment offers a hope of cure. We hold the view that even in the elderly, liver surgery is justified in carefully selected patients.

Acknowledgement

We wish to express thanks to Dr N. Nagasue who developed liver surgery in our hospital.

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Paper accepted 4 April 1987

Br. J. Surg. 1987, Vol. 74, June,
474–478

Pre-operative assessment of soft tissue sarcomas by computed tomography

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The current trend towards limb-sparing surgery in patients with soft tissue sarcomas has increased the need for accurate pre-operative assessment of the primary tumour. Tumour site, extent and relationship to bone and neurovascular structures determine whether adequate radical surgery is feasible or whether more limited excision as a part of multimodality treatment is appropriate. Pre-operative computed tomography (CT) was compared with operative findings in 38 patients with soft tissue sarcomas. CT prediction of muscle group involvement by tumour was correct in 95 per cent and prediction of major artery or vein invasion was correct in 92 per cent and 97 per cent respectively. Assessment of tumour relationship to major peripheral nerve was accurate for thigh sarcomas but was not possible in upper limb tumours. While CT confirmed frank bony involvement in two patients, it failed to distinguish between tumours closely adjacent to periosteum and those with periosteal invasion. Detection of residual or recurrent tumour nodules is less reliable; CT is most accurate before any surgical intervention.

Keywords: Soft tissue neoplasm, X-ray computed tomography, sarcoma

Computed tomography (CT) is now used in many centres in the management of soft tissue sarcomas. Of the imaging modalities currently available, CT is the most accurate for detection of pulmonary metastases[1,2] and is valuable for planning radiotherapy treatment fields to the primary tumour site[3,4]. CT assessment of the primary tumour before surgery provides useful anatomical information about the extent of the soft tissue sarcoma and its relationship to neurovascular and bony structures[5–11].

Table 1 *Site of soft tissue sarcoma*

Lower limb	
Thigh	18
Leg	1
Upper limb	
Arm	5
Forearm	3
Pelvic girdle	
Buttock	3
Groin	3
Neck	4
Trunk	1
Total	38

It is now well established[12–14] that radical local surgery as the sole treatment modality in the form of compartmental resection for soft tissue sarcomas of the limbs can, where this is possible, achieve local tumour control while allowing conservation of a useful limb. Enneking and colleagues[1,15] have defined such non-ablative procedures as adequate only when the planes of resection are separated from the tumour and its tissue or tissues of origin by at least one uninvolved anatomical layer. With radical radiotherapy as an adjunct to surgery, some centres have now demonstrated equally low rates of local recurrence with more limited local excision of the tumour and its surrounding envelope of reactive tissue[16,17]. This is important because in many patients the site and extent of the tumour do not permit ideal limb-conserving surgical procedures. Removal of all macroscopic tumour is desirable if radiotherapy is to have its maximum chance in sterilizing microscopic disease remaining within the compartment treatment volume[14].

With the current trend towards limb-sparing surgery, the need has arisen for pre-operative evaluation of the extent of the tumour so that the optimum surgical resection can be planned in order to minimize the possibility of local recurrence yet preserve maximum function of the limb[18]. This study attempts to determine the accuracy of CT in predicting the extent of the primary tumour and its relationship to bone and neurovascular structures by comparing pre-operative scans with surgical findings. The influence of CT in aiding operative planning is also evaluated.

Table 2 *Findings at surgical exploration compared with pre-operative CT assessment of soft tissue sarcomas. In nine patients CT evaluation of peripheral nerves was not possible and in three of these (all with upper limb tumours) major arteries and veins could also not be visualized*

Operative findings		Extracompartmental spread		Major artery involvement		Major vein involvement		Major nerve involvement		Bone involvement		Skin involvement		Subcutaneous tissue involvement	
		+	–	+	–	+	–	+	–	+	–	+	–	+	–
CT assessment	+	16	1	4	3	6	0	4	3	8	10	8	0	8	2
	–	1	20	0	28	1	28	0	22	1	19	0	30	2	15

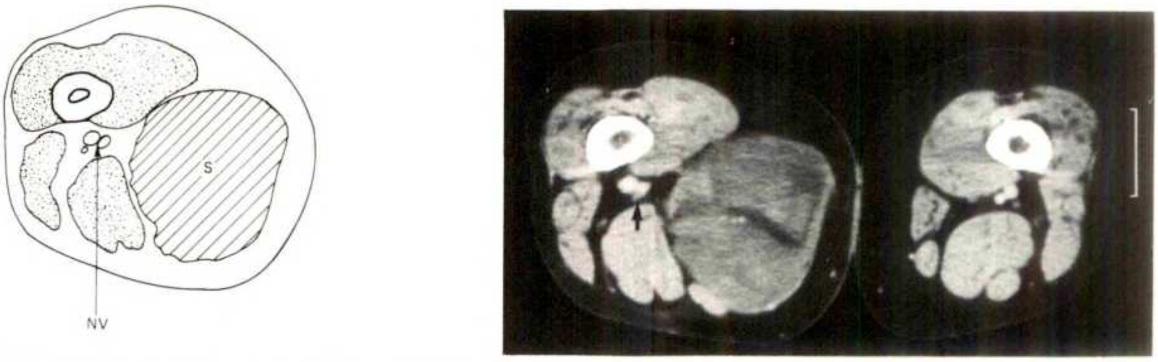

Figure 1 *Soft tissue sarcoma confined to the adductor muscle compartment of the right thigh. Radical compartmental resection with preservation of major neurovascular structures (arrowed) was possible*

Patients and methods

Thirty-eight patients with soft tissue sarcomas undergoing surgical exploration by one surgeon (G.W.) over a 2 year period 1984–1986 were assessed. For inclusion in the study, each patient was required to have undergone CT examination of the primary tumour site in the pre-operative period with scans available for review. The mean patient age was 51 years (range 16–80 years). The site of each tumour is shown in *Table 1*. Retroperitoneal sarcomas were excluded from this study.

At the time of CT examination only four patients had not undergone previous biopsy. In the remainder histological diagnosis had been established by needle or Trucut biopsy in four patients, by incision biopsy in eleven and by excision biopsy or enucleation in nineteen patients. Of this last group 14 had clinical evidence of residual or recurrent disease. As in most recently classified series, malignant fibrous histiocytoma was the most common histological type (16 of 38 tumours). The inability of CT to identify soft tissue sarcoma by histological type (apart from lipoma-like liposarcoma) is recognized[8,19,20] and we made no attempt to do so in this study.

The CT examinations of 29 patients were performed at the Royal Marsden Hospital, London using a Siemens Somatom DR2 scanner with a 5 s scanning time. Scans were performed at slice widths of 8 mm (4 mm in one patient) with a scan increment ranging from 8 to 30 mm depending on the size of residual tumour and the size of the region to be examined. Intravenous contrast (Urografin 370) was given as a 50 ml bolus followed by an infusion of 50–100 ml in 23 patients. Of the nine scans performed in other hospitals, intravenous contrast was given in only two patients.

CT scans were reviewed retrospectively by one radiologist (C.P.) who was unaware of the operative findings. CT scans were evaluated to determine (a) whether the primary tumour was confined to a single anatomical compartment or extended extracompartmentally and (b) its relationship to major arteries, veins, nerves, bone, subcutaneous tissue and skin. Muscle involvement was indicated by enlargement, inhomogeneity and alteration in contrast uptake by a muscle group and by obliteration of intra- and extracompartmental fat planes and thickening of fascial layers. Neurovascular and periosteal involvement were suggested by encirclement or direct contact with tumour, obliteration of a vessel lumen, and thickening of a neurovascular sheath.

A detailed record of operative findings with reference to tumour extent and involvement of surrounding structures was made at the time of surgery in each patient. CT and surgical findings were correlated both in the group where a particular structure was found at surgery to be involved, and in the group without such tumour involvement, so that false positive and false negative rates could be assessed. Where the anatomical structures under consideration could not be visualized on CT, these patients were excluded from evaluation (*Table 2*).

Results

CT was accurate in 36 of 38 patients (95 per cent) in predicting the individual muscle groups involved and whether the tumour was confined to or extended beyond a muscle compartment (*Figure 1*). In one patient with a tumour arising in the extensor compartment of the thigh, CT overpredicted involvement of vastus medialis muscle which was uninvolved and conserved at surgery (false positive rate 3 per cent). In a second patient with an adductor compartment tumour CT underpredicted involvement of adductor magnus muscle (false negative 3 per cent).

Relationship of tumour to major arteries was correctly predicted in 35 of 38 patients (92 per cent), including all four cases where tumour involved the artery. In the other three cases CT appearances suggested arterial involvement (*Figure 2*) but at surgery the artery could be dissected free without transecting tumour planes. Tumour relationship to major veins was correctly predicted in all but one patient (97 per cent accuracy).

In the lower limb CT correctly predicted the relationship of tumour to major peripheral nerves in all but one case where CT showed the sciatic nerve applied to the tumour but at surgery the tumour was dissected free of the nerve without difficulty. All four patients found at surgery to have sciatic nerve involvement were correctly predicted by CT (*Figure 3*). Thus in 29 patients

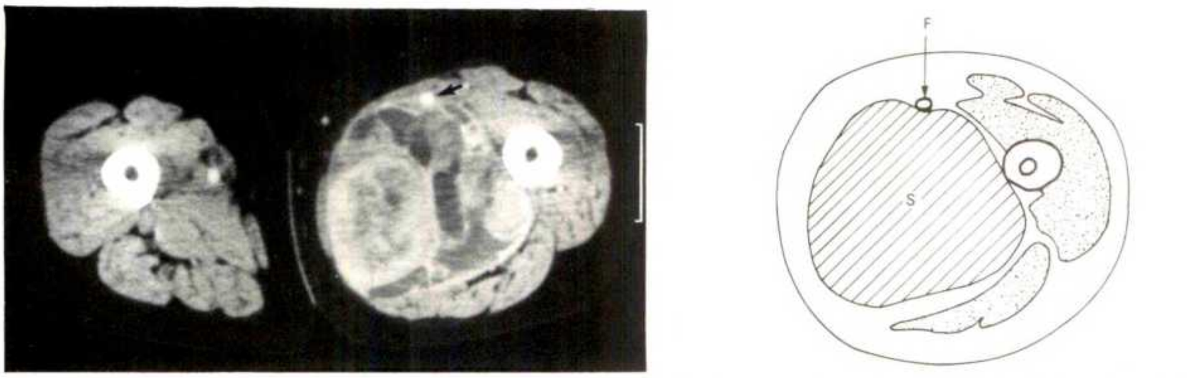

Figure 2 *Heterogeneous soft tissue sarcoma of medial left thigh. The femoral artery (arrowed) appears closely applied to the tumour pseudocapsule but at surgery was clear of tumour. Periosteal involvement was similarly overpredicted in this patient*

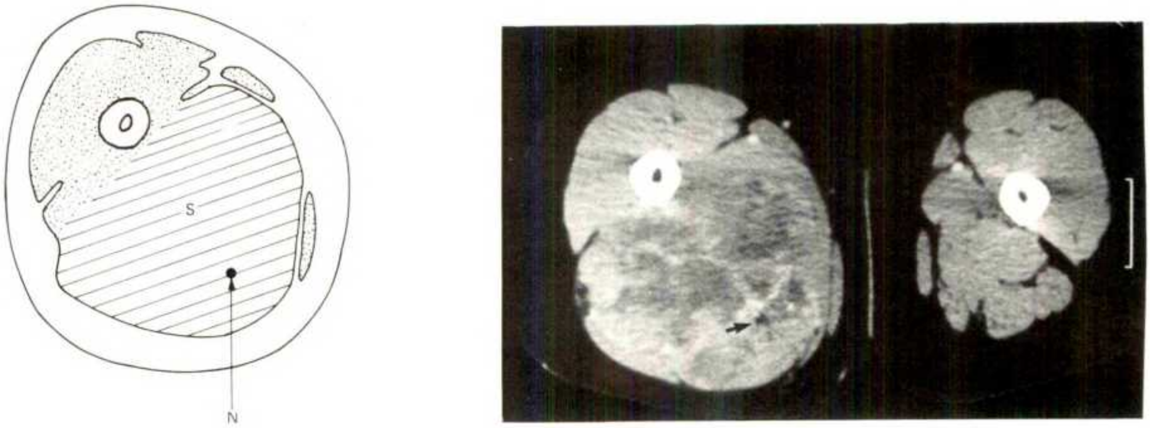

Figure 3 *Extensive soft tissue sarcoma of the right thigh involving adductor and hamstring compartments. The sciatic nerve (arrowed) is surrounded by tumour*

where the nerve was visualized, CT was 90 per cent accurate in predicting the relationship of tumour to nerve. However in eight upper limb sarcomas CT failed to demonstrate the peripheral nerves in six patients and in a seventh overpredicted radial nerve involvement.

Two patients with frank bony destruction by tumour were confirmed on CT. CT however failed to distinguish between tumours closely adjacent to periosteum and those with periosteal invasion and overall accuracy was only 70 per cent. Contact with periosteum was overpredicted in 10 patients (false positive 27 per cent) in whom a clear plane of dissection was found at surgery between tumour and periosteum (*Figure 2*). CT did not predict periosteal involvement in one patient (false negative 3 per cent) where stripping of periosteum *en bloc* with tumour proved necessary.

CT prediction of skin involvement was correct in all cases and CT was in addition able to identify skin changes secondary to previous radiotherapy or biopsy. However in patients who had been referred following inadequate tumour excision CT failed to distinguish between subcutaneous tumour nodules and surgical scarring in two patients. In a further two patients CT interpreted as tumour a small enhancing area which on surgical exploration was found to be scar tissue in one patient and a stitch abscess in the second (*Figure* 4).

Discussion

Wide experience with CT has accrued in specialist centres dealing with soft tissue sarcomas and its advantages over ultrasound[7,10], xeroradiography[9], and angiography[5] are now recognized. Whilst ultrasound and xeroradiography indicate tumour size they are of little value in assessing extracompartmental spread. CT has the advantage of demonstrating cross-sectional anatomy in great detail. Early reports[19] were less encouraging, but significant improvements in CT technology have had a positive influence on its usefulness in demonstrating tumour relationship to surrounding structures. Recent reports suggest that the greater contrast of magnetic resonance imaging[1,21] may provide even more accurate information but experience is still limited. Critical comparison of CT with detailed evaluation at the time of tumour resection has not been reported to date.

Our study demonstrates that pre-operative CT can accurately predict the individual muscles and fascial planes involved by soft tissue sarcoma and the presence of extracompartmental extension. Such information is helpful in determining whether radical compartmental resection is appropriate, or indeed feasible. Although clinical examination will often indicate reliably which compartment is primarily involved, considerable distortion and displacement of muscle groups may occur with large tumours.

With the use of intravenous contrast material, CT prediction of vascular involvement by tumour is sufficiently accurate to allow planned prosthetic replacement in those few cases where arterial resection is necessary. Resection of a major peripheral vein may usually be performed without reconstruction or significant postoperative morbidity. Angiography has been considered of value in distal limb tumours where CT resolution of smaller vessels may prove difficult[5]. As in other centres[5,7] we now reserve angiography for those cases where arterial

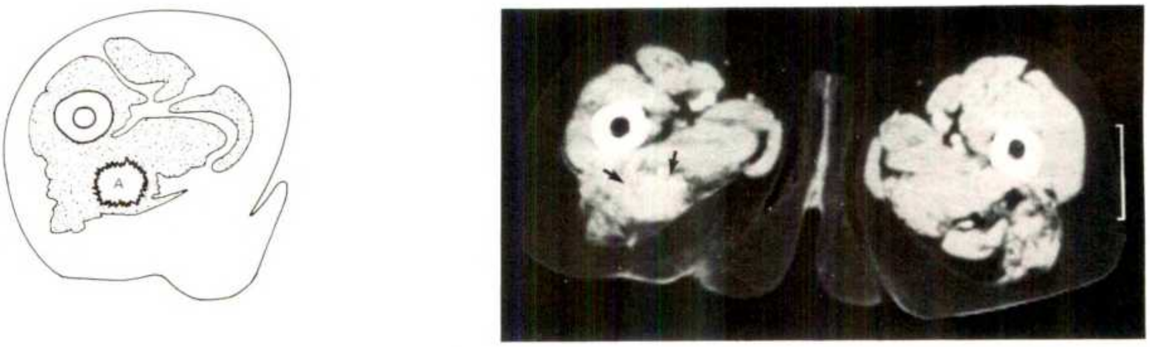

Figure 4 *Enhancing area (arrowed) diagnosed as tumour recurrence 6 months after resection of sarcoma of posterior right thigh. This proved on re-exploration to be a stitch abscess*

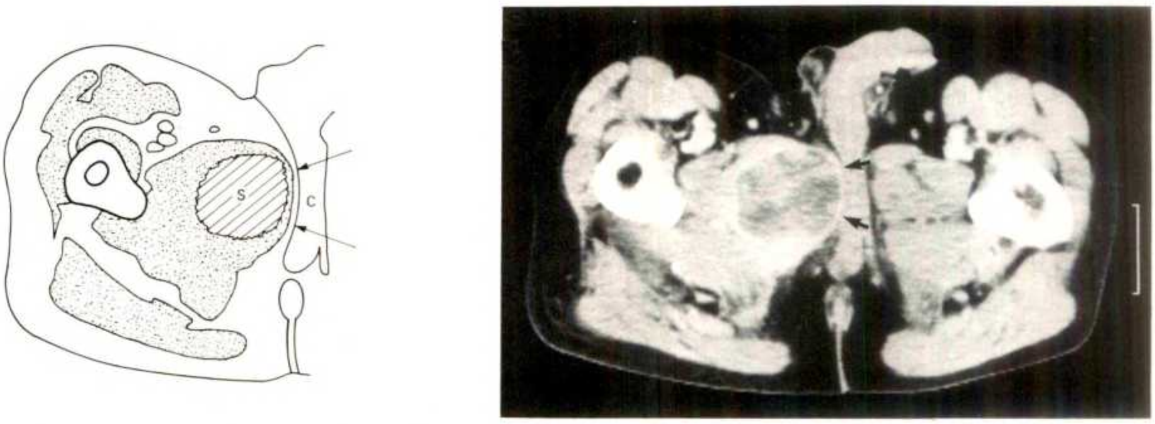

Figure 5 *Sarcoma extending into right groin region. A tissue plane (arrowed) between tumour and corpora of the penis (and between tumour and pubic ramus on other scans) was evident and a limb-sparing resection was feasible*

involvement is suspected on CT or where indicated for optimal placement of intra-arterial catheters for regional chemotherapy.

The difficulty in differentiating nerve or vessel invasion from close proximity of these structures to the tumour pseudocapsule has been recorded by Weekes and colleagues[20] who found poor correlation between CT assessment and operative findings in nine patients where surgical records were available. In our study CT accurately predicted tumour relationship to major peripheral nerve (principally the sciatic nerve in the thigh) in 24 of 25 lower limb/limb girdle tumours. In the forearm and leg however very little fat is present in intracompartmental soft tissue planes; peripheral nerves are smaller and are difficult to visualize when closely applied to tissue of similar radiological density. Neurological examination, knowledge of anatomical landmarks for each nerve and clinical and CT assessment of tumour site are of major importance with soft tissue sarcomas in the upper limb. Nerve conduction tests and electromyography are unreliable predictors of peripheral nerve involvement by tumour[1].

While conventional radiographs remain the first radiological investigation in bone sarcomas[1], bone destruction and periosteal reaction are rarely seen in soft tissue sarcomas. Our study illustrates the difficulty in distinguishing with CT between tumours closely adjacent to periosteum (where pressure within the soft tissue compartment obliterates the radiological plane between tumour and bone) and tumours adherent to periosteum either by reactive processes in the tumour pseudocapsule or by true malignant infiltration. Radiological factors such as beam hardening artefact and volume averaging effect[18] may also make evaluation more difficult. Isotope bone-scanning has been advocated[1,18] to determine involvement of periosteum. Because radioisotope is also taken up by tumour (and by recent scar tissue), a meticulous imaging technique is required with a high-resolution gamma-camera and using multiple projections.

Golding and Husband[2] compared CT appearances with surgical findings in 24 patients with soft tissue sarcomas and found prediction of operability correct in 92 per cent. The availability of effective adjuvant treatment e.g. radiotherapy and regional chemotherapy has extended the concept of strict operability as defined by Enneking[1,15]. In this respect CT is valuable in predicting the feasibility of adequate radical local surgery, or whether tumour extent and relationship to neurovascular and bony structures preclude more than marginal (extracapsular) resection or even debulking (intracapsular) surgery. In the present study operative planning was aided in 8 (21 per cent) of our patients, especially for tumours involving the pelvic girdle and groin where CT predicted either the need for hindquarter amputation or the feasibility of limb-sparing surgery (*Figure 5*). The prediction of need for *en bloc* resection of bone or artery in five patients allowed appropriate surgical preparation to be made.

The difficulty in evaluating with CT small-volume residual or recurrent tumour following excision biopsy has been documented[22] and our findings are in agreement with this. The detection of small tumour nodules in this situation may be impaired by scanning technique if a wide increment is used between slices, and the radiologist's attention must be directed to any area of clinical suspicion. In addition, a tiny nodule may be below the resolving power of the scanner. When a small area of abnormal tissue is identified, the distinction between scar, haematoma and tumour cannot reliably be made by CT (although CT-directed needle biopsy may establish a tissue diagnosis).

In conclusion, therefore, we advocate the use of pre-operative CT, with intravenous contrast enhancement, in all patients with soft tissue sarcoma in contributing information of value to a planned surgical procedure. We advise that the most useful time for CT assessment of a tumour suspected clinically of being a soft tissue sarcoma is before any surgical violation of tissue planes. The surgeon and radiologist should discuss the particular requirements in each patient so that scanning technique may if appropriate be modified to derive maximum information about the tumour.

Acknowledgements

We thank the Department of Medical Photography for their kind help with the illustrations.

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Paper accepted 25 October 1986

Br. J. Surg. 1987, Vol. 74, June, 479–480

Value of fine needle aspiration cytology in the diagnosis of soft tissue tumours: a preliminary study on the excised specimen

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The local behaviour of soft tissue sarcomas may be adversely affected by incorrect initial management. Therefore it is valuable to obtain a tissue diagnosis before treatment[1,2].

Although needle biopsy has potential advantages over open biopsy, it has been criticized because of problems in sampling and interpretation. We found that Tru-cut needle biopsy has a correct predictive accuracy of >90 per cent in the diagnosis of soft tissue lesions[3].

In this parallel study we assess the value of fine needle aspiration (FNA) cytology in 54 consecutive patients undergoing surgical resection of soft tissue tumours at the Royal Marsden Hospital.

Aspirates were taken from excised specimens and not *in situ*. Although this is an artificial situation, 'operator' sampling error was thereby minimized. FNA was carried by standard technique[4] with air-dried smears stained using May–Grünwald–Giesma.

Randomly labelled smears were reported 'blind' by two cytologists: cytologist A, a histopathologist with an interest in soft tissue tumours and cytologist B, a general surgeon with an interest in FNA. Neither was aware of clinical details or definitive histology. Each categorized smears as malignant, benign or inadequate and made specific diagnoses where possible. These findings were compared with routine histology diagnoses.

Results

The histological diagnoses are shown in *Table 1*. Forty-eight (88·9 per cent) were malignant. The accuracy of FNA diagnosis is shown in *Table 2*. Excluding inadequate smears, sensitivity of FNA was 62·5–75 per cent, specificity was 83·3–100 per cent, and overall predictive accuracy was 81–93 per cent.

Cytologist A

Of 37 smears reported as malignant, 36 were sarcomas whilst 1 was benign. Of six reported as benign, two were malignant. The remaining 11 were inadequate (1 proved to be benign and 10 malignant).

Cytologist B

All 30 smears reported as malignant were confirmed as sarcomas. Of 12 reported as benign, 8 were malignant. The remaining 12 were inadequate (2 proved to be benign and 10 malignant).

Table 1 *Definitive histological diagnosis*

Malignant (48)		Benign (6)	
Malignant fibrous histiocytoma	24	Infiltrating fibromatosis	3
Liposarcoma	7	Nodular fascitis	1
Synovial sarcoma	4	Myxoma	1
Dermatofibrosarcoma protuberans	2	Intramuscular haemangioma	1
Leiomyosarcoma	2		
Pleomorphic sarcoma	2		
*Others	7		

* Fibrosarcoma, rhabdomyosarcoma, alveolar soft part sarcoma, epithelioid sarcoma, malignant schwannoma, neurofibrosarcoma, embryonal sarcoma, 1 each

Table 2 *Percentage accuracy of cytological diagnosis*

	Cytologist A	Cytologist B	'Pooled' results
Sensitivity	75·0	62·5	85·4
Specificity	83·3	100·0	83·3
Predictive value of positive diagnosis	97·3	100·0	97·6
Predictive value of negative diagnosis	66·7	33·3	71·4
Overall accuracy	93·0	81·0	93·9
Inadequate for diagnosis	20·4	22·2	9·3

Overall accuracy excludes those inadequate for diagnosis
'Pooled' results are taken from combining results of cytologists A and B as a 'panel', taking the most aggressive diagnosis of the two

Identical correct diagnoses were made in 25 sarcomas (52·1 per cent) and 2 benign lesions (33·3 per cent). When inadequate smears were excluded the concordance rates increased to 75·5 per cent and 66·7 per cent for malignant and benign lesions respectively. Correct subtyping of smears diagnosed as sarcomas was made in 66·7 per cent by cytologist A and 56·7 per cent by cytologist B.

Discussion

While the need for a pre-treatment tissue diagnosis for soft tissue tumours is not questioned, the optimum method of biopsy remains controversial.

A pilot study from Lund on 178 excised tumours, reported a sensitivity of 80 per cent in diagnosing sarcoma[5]. In their second study of 112 patients these cytologists found that preoperative FNA was valuable in planning margins of resection. The clinically anticipated extent of surgery was reduced in 28·4 per cent and increased in 4·9 per cent[6]. Layfield *et al.*[7] were able to diagnose 94·3 per cent of 53 sarcomas with a false positive rate of 2·2 per cent in a total series of 136. In the above studies less than 40 per cent of patients had sarcomas.

About 20 per cent of the smears in the present series were inadequate. A similar source of error occurs in 10·3 per cent of open biopsies[8], 16 per cent of Tru-cut biopsies[3] and 9·5–17 per cent of FNAs[5–7]. The inadequacy rate in the present series is worrying, especially as the aspirates were taken from the excised specimen and interpreted by enthusiasts. However, in the intact patient the tumour is fixed by the surrounding tissues, and this may permit 'cleaner' aspiration.

The high rate of false negative diagnosis (18·5 per cent) may be ascribed to a reluctance to overdiagnose sarcoma in borderline smears.

This paper is based on a presentation to the British Society of Clinical Cytology, Durham University in September 1986

0007–1323/87/060479–02$3.00

Although the sensitivity of FNA was less than that of Tru-cut biopsy[3], the predictive value of a positive diagnosis was more than 90 per cent for both techniques. The overall accuracy compares favourably with that of open biopsy (80 per cent)[1]. When used together these diagnostic aids, taken in conjunction with the clinical findings, may permit the extent of surgery to be tailored to the true nature of individual lesions with minimal risk of dissemination.

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Paper accepted 12 December 1986

Br. J. Surg. 1987, Vol. 74, June, 480–481

Role of ultrasound in the diagnosis of liver metastases before surgery for large bowel cancer

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Immediate mortality and morbidity following surgery for colorectal cancer have improved following developments in surgical technique but there is no other evidence that the long-term survival following successful surgery has improved in the last 30 years; survival is closely related to the presence of hepatic metastases. The failure of surgery to improve the prognosis has led to trials of adjuvant treatment and there is now evidence that liver perfusion following surgery may improve the prognosis when no hepatic metastases are identified at laparotomy and provided there is no histological evidence of lymph node involvement (Dukes' B tumours)[1]. Adjuvant therapy will only be successful if metastases are small. There may, however, be a population with liver metastases of a significant size, i.e. more than microscopic, which, because they are located deep in the liver, cannot be palpated; the presence of such a population would prejudice successful liver perfusion. We wondered whether such a population could be identified before surgery by ultrasound liver scanning.

Patients and methods

During the period of study, 1982–1983, patients admitted for elective surgery for large bowel cancer under the care of two surgeons at two District General Hospitals underwent pre-operative ultrasound scanning. Ultrasound scanning was mainly performed by consultant radiologists: in Wolverhampton a Nuclear Enterprises/GL 4290 real time machine was used; in Guildford, a linear array Toshiba Sonolayer C (Model SAC 12) real time with separate B scanner was used. The result of this scanning was not available to the surgeon at the time of laparotomy when the liver was carefully palpated for the presence of metastases; biopsy was performed for confirmation of all deposits. The two consultant surgeons involved in the study performed virtually all the surgery. Patients have subsequently been followed at 3 month intervals for evidence of the development of liver metastases.

Results (*Table 1*)

We studied 195 patients: in 2, in whom ultrasound was negative, the liver could not be palpated; 152 (77·9 per cent) had no metastases identified either by ultrasound or at laparotomy; 15 (7·6 per cent) had metastases identified both by ultrasound and at laparotomy. Ultrasound failed, however, to identify metastases present at laparotomy in 14 (7·2 per cent) patients; 5 (2·6 per cent) had metastases when ultrasound was suspicious but not definite. One patient had liver cysts with ultrasound being reported as uncertain. In two patients, laparotomy was uncertain but ultrasound was negative; one of these patients had metastases at a further laparotomy 4 months later while the other (aged 88) died 1 year later, there being no post-mortem examination. Both ultrasound and laparotomy were uncertain about one further patient in whom there was no evidence of metastases at ultrasound 6 months later. Three patients were reported as ultrasound uncertain with a negative laparotomy; one had haemangiomas, the second had a negative ultrasound at 6 months and the third died within 1 year, without post-mortem examination. No patient was confidently identified as having metastases on ultrasound when laparotomy was negative.

Table 1 *Results of investigations for liver metastases in patients undergoing surgery for large bowel cancer*

Laparotomy findings	Pre-operative ultrasound examination			
	No	Yes	Suspicious	Uncertain
No	152 (77·9)	0	—	3*
Yes	14 (7·2)	15 (7·6)	5	—
Cysts	—	—	—	1
Uncertain	2	—	—	1†

Figures in parentheses are percentages
*One patient haemangiomas, one negative ultrasound at 6 months, one dead at 1 year without post-mortem
†Negative ultrasound at 6 months
In two patients the liver was not palpated

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Discussion

In view of the apparent success of postoperative liver perfusion[1] it is important to assess the liver as accurately as possible for clinically occult metastases not only as an index of prognosis but also because the presence of metastases would prejudice the success of liver perfusion potentially discouraging its use.

In 1982 Taylor and Lamb[2] correctly identified 13 out of 15 patients with liver metastases in 100 patients scanned before large bowel surgery; there was one so-called false positive but no further data as to whether this patient subsequently developed liver metastases. In the same year, Finlay *et al.*[3] studied 43 patients in the immediate postoperative period and identified by ultrasound 5 of 6 patients found to have metastases at laparotomy; CAT scanning identified all 6 patients. Two years later, 11 of the remaining 37 patients were considered to have clinical evidence of liver metastases; serial scanning over the 2 year period identified metastases in 3 of these patients by ultrasound and 9 by CAT scanning. In a further study[4] 35 patients who had undergone apparently curative resection for colorectal carcinoma were scanned in the immediate postoperative period; on the basis of these investigations patients were considered to have a disease-free liver or to possess occult hepatic metastases (that is, hepatic metastases not detected by the surgeon at laparotomy). The accuracy of the initial scanning was determined as a result of progressive enlargement of hepatic lesions demonstrated by sequential imaging. Eleven patients were thought to have occult hepatic metastases and ten of these developed extensive metastases during the follow-up period of 2 years. More recent studies[5,6] do not dwell on the possibility of identifying a population by ultrasound which cannot be identified at laparotomy.

The positive identification of liver metastases before surgery may provide valuable information when determining the management of individual patients with colorectal cancer, but we have failed to identify a population of patients with occult metastases by ultrasound scanning; indeed, there was a false negative rate of 7·2 per cent. This false negative rate, however, compares well with Pain *et al.*[7] who had a false negative rate of 56 per cent, only diagnosing by ultrasound 11 of 25 patients found to have metastases at laparotomy; they did, however, identify one patient who had metastases found at the subsequent post mortem which had not been found by the surgeon at laparotomy. Finlay and McArdle claimed to identify occult metastases initially by CAT scanning[3] but in their second paper[4] it is not clear whether this was a result of ultrasound or CAT scanning. Unfortunately, as they admit, CAT scanning is expensive and time consuming; they considered it to be a technique unsuitable for routine clinical use. We feel that if their results can be confirmed, the prognostic value would be such that it may be suitable for routine clinical use; we also agree with their suggestion that simple techniques should be developed and perhaps the hepatic perfusion index may be the answer[8].

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Paper accepted 5 December 1986

Br. J. Surg. 1987, Vol. 74, June, 481–482

Changing distribution of adenocarcinoma of the stomach

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Although the incidence of carcinoma of the stomach is decreasing there is a clinical impression that tumours of the cardia are becoming more common. Unfortunately Cancer Registry data on the distribution of tumours within the stomach is unsatisfactory. Therefore, we have examined all pathology records at one hospital from two 5-year periods with a 25-year interval. Cases where biopsy material only was available have been excluded, thus only post mortem and surgical resection specimens which allow definition of the site and extent of the tumour within the stomach have been studied.

Patients and methods

All pathology reports of adenocarcinoma of the stomach or lower oesophagus at St. George's Hospital, London, during the periods 1951–55 and 1981–85 were reviewed. Each case was classified according to site as upper, middle or lower third of the stomach and pathologically staged according to TNM criteria. The statistical analyses for changes in the distribution within the stomach were by standard χ^2 tests for trend.

Results (*Table 1*)

There were 113 cases in the period 1951–55 (65 surgical specimens, 48 post mortems) and 101 cases from 1981–85 (82 surgical specimens, 19 post mortems). Seventeen cases during 1951–55 and seven during 1981–85 could not be classified according to site because the tumours were extensive. It was assumed that their site of origin was similar in proportion to the

Table 1 *Number of cases of gastric carcinoma by site, age and sex*

Site		Age (years)					Sex			
		<50	50–59	60–69	70–79	80–89	Male	Female	Cases	Total
Upper third	1951–55	2	6	5	4	0	11	6	10	17*
	1981–85	3	7	16	9	2	27	10	7	37
Middle third	1951–55	2	12	9	6	1	18	12	12	30
	1981–85	0	2	8	7	1	13	5	4	18
Lower third	1951–55	5	14	20	7	3	26	23	17	49
	1981–85	3	11	8	11	6	21	18	5	39
Diffuse	1951–55	2	6	4	4	1	12	5	9	17
	1981–85	1	0	1	4	1	4	3	3	7

other cases and these were excluded from further analysis (*Table 1*). There was an increase in carcinomas of the upper third over this period from 17 (18 per cent) during 1951–55, to 37 (39 per cent) by 1981–85 ($P = 0{\cdot}01$). This was accompanied by a corresponding reduction in middle-third (from 31 to 19 per cent) and lower-third neoplasms (51 to 47 per cent). The male:female ratio was highest in the upper third cases and decreased from upper to middle to lower third tumours in both periods ($P < 0{\cdot}05$) but there was no variation in age according to site in either period. There were only four T_1 cases during 1951–55 but twelve were seen in the period 1981–85 whereas the number of T_4 cases decreased from 38 to 27. There was no difference in 'T' or 'N' stage between the different sites.

Discussion

The proportion of gastric tumours occupying the proximal stomach has been variously reported between 1 and 34 per cent[1,2] but 9 per cent is probably a more representative figure[3]. In the present series 39 per cent occurred in this region during the period 1981–85 which was a significant increase from the earlier period thus supporting the clinical impression that carcinoma of the cardia has become more common. Two studies from the USA have also reported an increase in the proportion of carcinomas arising in the proximal stomach[2,4]. In England and Wales the number of registered cases of carcinoma of the cardia has increased steadily from 342 in 1968 to 1114 in 1982 but it is impossible to draw firm conclusions from this data since 968 and 7792 cases respectively did not have the site of the tumour within the stomach specified.

It is generally believed that the decreasing incidence of gastric cancer is due to a decrease in Lauren's 'intestinal' type[3] while the incidence of the 'diffuse' type remains unchanged[5] although there is contradictory evidence[6]. It might be expected that 'diffuse' tumours would now predominate in the upper stomach but carcinoma of the cardia is usually of the 'intestinal' type[3]. The tumours of the proximal stomach during 1981–85 were therefore reviewed by a histopathologist and were classified as 'intestinal' in 24/32, 'diffuse' in 6/32 and 'mixed' in the remainder suggesting that 'intestinal' tumours remain most common in the cardiac region.

The reason for the increase in tumours of the proximal stomach is unclear but it may be relative. If the declining incidence of gastric carcinoma is due to fewer tumours in the distal two thirds of the stomach, proximal tumours will appear more common even if their absolute incidence is unchanged.

Acknowledgements

We are grateful to Dr M. G. Cook for allowing us to study the Department of Histopathology records, Mrs Janis Davidson for help with the statistical programme, and Mrs Helen Jones for providing Cancer Registry data.

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Paper accepted 3 December 1986

Announcement

Nipple preservation during mastectomy (Br J Surg 1987; 74: 58–61)

Mr A. E. Kark and Mr M. W. Kissin have written to the Journal about the above paper to say that as a consequence of the long delay between the original pathological review and the final preparation of the definitive manuscript after the original report (*Br J Surg* 1982; **69**: 295) the name of Dr E. M. Thompson was inadvertently omitted from the list of authors.

Our rules at *The British Journal of Surgery* are clear: we cannot be responsible ourselves for redressing an error such as this. However, we publish this note both in fairness to Dr Thompson and to remind authors how important it is to make sure that all those involved in a scientific project get due recognition.

Br. J. Surg. 1987, Vol 74, June, 483–487

Primary gastric lymphoma

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This is a population-based review of 153 cases of primary gastric lymphoma. Sixty-seven (43 per cent) were histologically reviewed using the Kiel classification. There were no significant differences between reviewed and unreviewed cases. Ninety-seven per cent of all cases were of the non-Hodgkin's type. The annual incidence was constant at 1·2 per cent of gastric malignancies. The mean age was 60 years and the male to female ratio 1:8. Presenting symptoms were similar to those of gastric cancer. Twenty-one per cent had a palpable mass but one-third of these were amenable to a potentially curative resection. Some 66 per cent were resectable and 58 per cent had a macroscopic clearance of tumour. TNM stage and absolute tumour size were significant prognostic factors ($P<0{\cdot}005$ and $P<0{\cdot}05$ respectively) but the Kiel classification was not. The overall 5 year survival was 24 per cent. Apart from 10 patients whose only anti-tumour treatment was radiotherapy (5 year survival 36·9 per cent) no patient who did not have curative surgery survived 5 years. The 5 year survival for curative resection was 34 per cent and for curative resection plus radiotherapy was 43·5 per cent (45 and 73·4 per cent for the node negative cases respectively). A laparotomy is essential; 'curative' surgery possibly with adjuvant radiotherapy offers the best hope for cure.

Keywords: Stomach lymphoma, prognostic factors, radiotherapy, Kiel classification

Primary gastric lymphoma is the commonest extra nodal primary site for non-Hodgkin's lymphoma and yet is itself uncommon. The biological behaviour appears to be different from either gastric carcinoma or primary nodal lymphoma[1]. Because of its rarity, it has been difficult for any one centre to collect sufficient cases for a substantive review and in addition only the more recent reviews have used modern morphological and immunological classifications[2]. Most reports analyse the gastrointestinal tract as a unit and it is not always possible to separate out the data which are exclusive to gastric lymphoma. To provide more accurate clinical and epidemiological data the records of gastric lymphoma patients registered with the Birmingham Regional Cancer Registry have been reviewed.

Patients and methods

During the period 1957–1976 the Birmingham Regional Cancer Registry had been collecting data from the whole of the West Midlands region (a population base of just over 5 million). Doubtful cases of lymphoma were reviewed before being included. For this study, histological blocks were requested from the appropriate pathology departments and when available 2 μm sections were all reviewed, using the Kiel classification[3], by one pathologist (J.C.). When necessary classification was advanced by routine immunoperoxidase methods[4].

All the registry records were reviewed. Cases with disease beyond the abdominal cavity were excluded. The remainder were accepted as primary gastric lymphomas on the opinion of the surgeon conducting the laparotomy or the pathologist at the post mortem. The advanced cases all had a substantial gastric lesion constituting the main tumour mass and only local nodes. Five cases had small metastases in the liver (two), spleen (one), or omentum (two). Three cases had direct invasion into liver (two), or spleen and pancreas (one).

The age, sex, duration and type of presenting symptoms, presence of mass, size of primary, stage of disease, type of therapy and survival were analysed. The stage was defined by the modified TNM classification as used for carcinoma[5]. Age-adjusted survival rates[6] were used and statistical comparisons made using Peto's log rank method[7]. All results were compared with the Birmingham Registry data for carcinoma of the stomach for the same period.

Results

One hundred and fifty-five patients with primary gastric lymphoma were recorded between 1957 and 1976.

Histology. Sixty-seven patients (43 per cent) were reviewed. Two (3 per cent) were carcinomas and were excluded from all subsequent analyses. No pseudolymphomas were identified. Distribution within the Kiel classification is shown in *Table 1*. Six cases were originally classified as Hodgkin's disease. Three were reviewed. One was confirmed to be Hodgkin's, one was lymphoplasmacytoid and one immunoblastic. One case, originally classified as reticulosarcoma, was found to be Hodgkin's. Five cases of Hodgkin's remained.

There were no significant differences between those cases reviewed and those not reviewed in sex, mean age, or stage. There were, however, variations in the distribution of stage within treatment groups. These are discussed later.

Presenting symptoms. The most common were abdominal pain (70 per cent) and weight loss (15 per cent) (*Table 2*). The median duration of symptoms (3·2 months) is similar to carcinoma (2·7 months).

Signs. Only one patient complained of a mass, yet 32 (21 per cent) had a palpable mass. Of those patients who had potentially curative surgery, 12 (14 per cent) had a palpable mass. Twenty-seven (18 per cent) were admitted as emergencies; fourteen with haematemesis and melaena, and five with perforation.

Incidence. The average number of cases per year was 7·7, which represented 1·2 per cent of all gastric malignancies with histological proof. The incidence was constant over this period except for 19 cases in 1974. The average annual rate was 1·5 per million population. Gastric lymphoma comprised about 40 per cent of all gastrointestinal lymphoma occurring in the West Midlands region.

0007–1323/87/060483–05$3.00

Sex. Distributions by sex, age and stage, are shown in *Table 3*. The male to female ratio was 1:8, in carcinoma it was 1:4.

Age. The mean age was 60·1 years, less than that seen for carcinoma (67·5). The range from 9 to 85 included a higher proportion of cases under 35 years than is seen with carcinoma, 3·9 per cent *versus* 0·02 per cent.

Stage. Most cases (96 per cent) could be staged. There were 44 stage I or II, 39 stage III, 13 stage IVA and 51 stage IVB, giving a distribution of 29, 25, 8 and 33 percent respectively. Six patients (4 per cent) had a 'curative' resection but the degree of nodal involvement was not known.

Treatment. One hundred and thirty-four (88 per cent) had a laparotomy. One hundred and one (66 per cent) were resectable and only thirteen of these were considered merely palliative, thus 58 per cent had a macroscopic clearance of disease and so a potentially curative resection. Twenty-seven (31 per cent) of the 'curative' resections received radiotherapy (mean dose 2800 rad given via high voltage X-ray, cobalt 60 or linear accelerator). One other patient had both radiotherapy and chemotherapy and one patient received adjuvant chemotherapy. Of the 13 palliative resections 4 received radiotherapy and 1 both radiotherapy and chemotherapy. Ten patients received radiotherapy and seven chemotherapy (with or without radiotherapy) as the sole anti-tumour treatment. Thirty-five (23 per cent) had no anti-tumour treatment. The postoperative mortality was 11 per cent (10/88) for curative resections' and 31 per cent (4/13) for palliative resections.

Cause of death. Of 120 patients who died within 5 years, 14 (12 per cent) were postoperative deaths and 93 (78 per cent) died of lymphoma. Eleven (9 per cent) died of other causes, seven with lymphoma present. Of the 33 patients who survived more than 5 years, 21 have died, 10 from lymphoma.

Survival. The crude overall 5-year survival was 20·9 per cent and the age adjusted rate 24 per cent. The Kiel classification was not prognostic. The reticulum cell sarcoma/lymphosarcoma classification was also not prognostic (21·7 and 25·9 per cent 5-year survival respectively).

Staging had prognostic value ($P<0·005$) (*Figure 1* and *Table 4*). Within each stage there were no significant differences in survival between the reviewed and unreviewed cases (*Table 4*). Size has a significant relationship to survival, 63 per cent for <5 cm and 8 per cent for >5 cm at 5 years ($P<0·05$) for the 37 cases where these data are known.

Table 5 shows the effect of treatment on survival. Thirty-five patients who had no anti-tumour treatment all died within 5 months. None of the 20 patients who had palliative surgery or chemotherapy were alive at 5 years (median survival <4 months). Ten patients had radiotherapy alone and three were alive at 5 years. Apart from these three all the other twenty-nine survivors at 5 years initially had a 'curative' resection. In this group there appears to be an improvement in survival when adjuvant radiotherapy is used even in these relatively modest doses (mean 2800 rad) (*Figure 2*). However, the numbers are small and this difference is not significant ($P>0·25$). This was not a randomized study and there must have been selection in allocating patients for radiotherapy. Most studies argue that patients offered radiotherapy would be expected to have a worse prognosis than the surgery only group. The data support this. *Table 5* shows that in the 'curative' resection group those receiving

Table 2 *Presenting symptoms*

	Lymphoma		Carcinoma	
	n	Percentage	*n*	Percentage
Pain (including dyspepsia)	107	69·9	11 517	45·4
Weight loss	23	15·0	6794	26·8
Vomiting	22	14·4	6422	25·3
Anorexia	10	6·5	4224	16·6
Dysphagia	7	4·6	2091	8·2
Mass	1	0·7	307	1·2
Bleeding and anaemia	13	8·5	5814	22·9
Flatulence	4	2·6		
Malaise and lassitude	5	3·3		
Bowel change	3	2·0		
Other	—	—		
Not known	7	4·6	2946	11·6
Total number of patients	153		25 376	

The two distributions are the percentages of each symptom in each group. The categories are not mutually exclusive.

Table 1 *Histological classification of reviewed cases with age-adjusted 5 year survival*

				5-year survival	
Classification	*n*	Percentage of total reviewed	Percentage of all cases	*n*	Rate (%) (age-adjusted)
High grade	30	46·1		7	27·3
Immunoblastic	10	15·4		5	55·6
Lymphoblastic	6	9·2		—	—
Centroblastic	6	9·2		—	—
Histiocytic	1	1·5		1	100·0
High-grade unclassifiable	7	10·8		1	21·4
Low grade	33	50·8		7	24·3
Immunocytic	15	23·1		—	—
Lymphocytic	7	10·8		3	51·1
Centroblastic-centrocytic	9	13·8		2	24·1
Centrocytic	2	3·1		2	100·0
Hodgkin's	2	3·1		—	—
Total classified as lymphoma	65	100·0	41·9	14	25·0
Changed to carcinoma	2		1·3	—	—
Total reviewed	67		43·2		
Not reviewed	88		56·8		
Total treated	155		100·0		

The two cases, both female, where the diagnosis was changed to carcinoma are excluded from all subsequent tables

Table 3 *Distributions by sex, age and stage for high grade and low grade lymphoma, Hodgkin's disease and not-reviewed cases*

		Sex						Stage							
		Males		Females		Age		I and II		III		IV		Not known	
	Total	*n*	Percentage	*n*	Percentage	Mean	Range	*n*	Percentage	*n*	Percentage	*n*	Percentage	*n*	Percentage
High grade lymphoma	30	20	66·7	10	33·3	58·5	9–84	7	23·3	7	23·3	15	50·0	1	3·4
Low grade lymphoma	33	20	60·6	13	39·4	60·8	34–85	11	33·3	13	39·4	7	21·2	2	6·1
Hodgkin's disease	2	1	50·0	1	50·0	72·5	62–82	—	—	1	50·0	1	50·0	—	—
Total reviewed	65	41	63·1	24	36·9	60·1	9–85	18	27·7	21	32·3	23	35·4	3	4·6
Not reviewed	88	57	64·8	31	35·2	60·1	17–85	26	29·5	18	20·5	41	46·6	3	3·4
Total	153	98	64·1	55	35·9	60·1	9–85	44	28·8	39	25·5	64	41·8	6	3·9

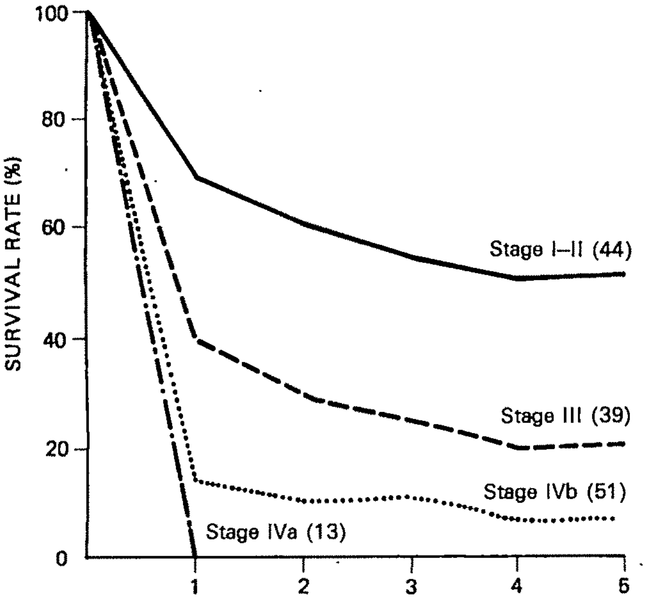

Figure 1 *Effect of staging on survival: age adjusted survival rates*

radiotherapy have a much higher proportion of node positive cases than those receiving surgery alone: 16/23 (70 per cent) *versus* 22/57 (39 per cent).

The radiotherapy group appears to have a better survival even if postoperative deaths are excluded (*Figure 2*). In the reviewed group there is a statistically significant survival benefit at 1 year for patients treated with radiotherapy after 'curative' resection ($0{\cdot}001<P<0{\cdot}01$) but not overall ($0{\cdot}1<P<0{\cdot}2$) (*Figure 3*). This is despite a higher proportion of node positive cases in the radiotherapy group (*Table 5*).

Discussion

This is the largest series of gastric lymphomas presented using a modern classification.

The distribution of subtypes of lymphoma in our series is comparable to that of Lennert[3] in his series of non-Hodgkin's lymphoma from many sites, but certain differences are present. Lennert reports low-grade lymphomas twice as frequently as those of high-grade histology. In this series high and low-grade lesions are present in approximately equal numbers. Especially prominent among these lymphomas were immunocytic lesions (23·1 per cent), which account for 18·6 per cent of Lennert's total series. In addition, there were relatively more immunoblastic neoplasms. Some of these differences may be accounted for by discrepancies in diagnosis between the reviewed specimens and those which were not available. It is reassuring that the percentage of high-grade unclassifiable lymphomas approximates to that in Lennert's collection (10·8 and 9·8 per cent, respectively).

Table 4 *Survival rates by stage of disease and review status*

	All cases		Reviewed		Not reviewed	
Stage	Total cases	5 year survival (age-adjusted)	Total cases	5 year survival rate	Total cases	5 year survival rate
II	44	50·7	18	56·6	26	46·7
III	39	20·9	21	16·7	18	25·7
IV	64	6·0	23	10·6	41	3·3
Not known	6	36·1	3	0·0	3	73·0
Total	153	24·0	65	25·0	88	23·5

The incidence of gastric lymphoma in the literature is 3 per cent of all gastric malignancies with some suggestion that the proportion has risen to 8–11·5 per cent[1]. In this series the incidence up to 1976 was 1·2 per cent. The higher figures in other series probably represent the selection bias of referral centres. The mean age and sex ratio of our data are both in the middle of the published ranges.

We have found no clinical features that distinguish gastric lymphoma from carcinoma but would stress that the presence of a mass in this disease by no means excludes resectability with hope of cure, although size of primary proved to be prognostic.

The most important prognostic factor in this series was stage. All studies have shown that limited disease carries a better prognosis than extensive disease. The classifications used, however, are not consistent. The Ann Arbor system[8] devised for Hodgkin's disease is not suitable for gastric lymphoma which is mostly of the non-Hodgkin's type. Musshoff[9] introduced a modification for Ann Arbor stage II disease to differentiate between local nodal involvement (II 1E) and more distant spread to para-aortic nodes (II 2E). This latter group of nodes would not be part of a conventional gastrectomy and involvement of para-aortic nodes in gastric carcinoma carries a very poor prognosis[10]. Patients with stage II 2E disease fare significantly worse than stage II 1E disease[11]. The behaviour of lymphoma in this respect is, therefore, very similar to carcinoma. Lim *et al.*[12] found the TNM system applicable to carcinoma to be prognostic in lymphoma. This study also confirms the prognostic value of the TNM system for lymphoma.

A comparison of gastric lymphoma with carcinoma shows that stage for stage lymphoma has a much better survival than

Table 5 *Survival rates by treatment and nodal status for all cases, reviewed and not reviewed*

	All cases 5-year survival			Reviewed 5-year survival			Not reviewed 5-year survival		
	Total	*n*	Rate (age-adjusted)	Total	*n*	Rate (age-adjusted)	Total	*n*	Rate (age-adjusted)
Curative resection	59	17	33·6	26	5	23·7	33	12	41·6
Node negative	35	14	45·0	12	4	40·7	23	10	48·7
positive	22	3	17·3	13	1	10·4	9	2	27·8
Not known	2	0	0·0	1	0	0·0	1	0	0·0
Curative resection + radiotherapy	27	11	43·5	15	6	42·1	12	5	45·6
Node negative	7	5	73·4	5	4	82·1	2	1	51·7
positive	16	4	27·5	8	2	27·3	8	2	27·7
Not known	4	2	54·2	2	0	0·0	2	2	100·0
Curative resection* + chemotherapy (± radiotherapy)	2	1	58·5	1	1	100·0	1	0	0·0
Palliative resection	8	0	0·0	3	0	0·0	5	0	0·0
Palliative resection and adjuvant therapy	5	0	0·0	1	0	0·0	4	0	0·0
Radiotherapy	10	3	36·9	5	2	49·9	5	1	25·3
Chemotherapy (± radiotherapy)	7	0	0·0	4	0	0·0	3	0	0·0
No anti-tumour treatment	35	0	0·0	10	0	0·0	25	0	0·0
All cases	153	32	24·0	65	14	25·0	88	18	23·7

* The reviewed case was node negative and the case not reviewed was node positive

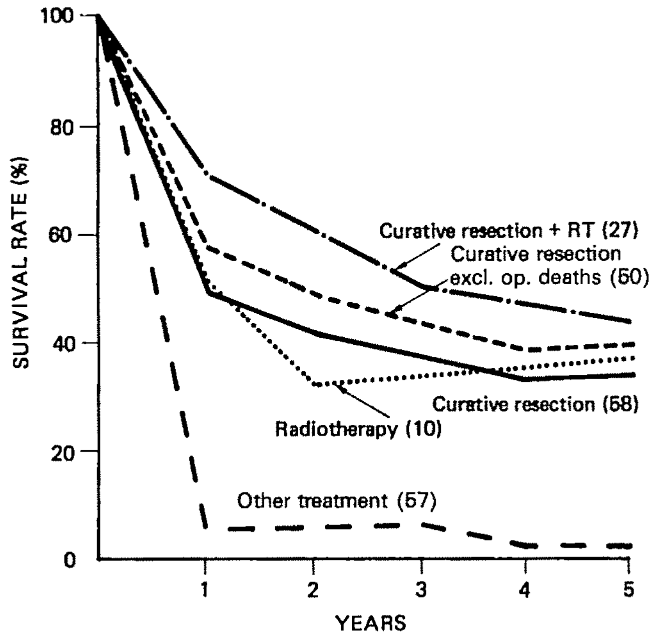

Figure 2 *Effect of radiotherapy on survival*

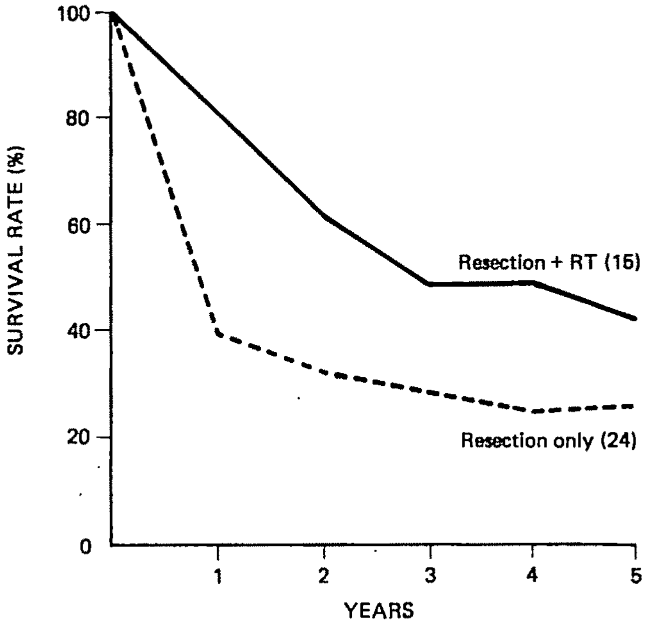

Figure 3 *Effect of radiotherapy on survival. Curatively treated–reviewed cases only, excluding postoperative deaths*

carcinoma particularly for the more advanced stages, for example stage III (21 *versus* 8 per cent at 5 years). Some of this effect may be due to the increased responsiveness of gastric lymphoma to radiotherapy. However, there would appear to be an inherently better prognosis for lymphoma, for example, in stage II (46 *versus* 30 per cent) and stage III (17 *versus* 8 per cent) when radiotherapy patients are excluded.

An important prognostic factor which relates to stage is the size of the primary, this confirms the finding of Dworkin *et al.*[11]. However, contrary to his study there was no effect of sex or age. Other studies have shown the Kiel classification to be prognostic[11,13,14] but this is not confirmed in the study. Low grade lymphomas present at an earlier stage[11] but despite this the overall survival is no better. The numbers in each subgroup were too small to enable firm conclusions to be drawn, however the low-grade immunocytic group (15 cases) has a poor survival (no survivors at 5 years) while the high-grade immunoblastic group (10 cases) has an age-adjusted 5-year survival of 55·6 per cent.

The best treatment for this disease is disputed. The only proven treatment of benefit in the literature is surgical resection[15]. Our own data strongly support this: apart from three patients who received radiotherapy alone the remaining twenty-nine long-term survivors initially had a curative resection. Our resectability rate of 66 per cent is higher than that found for carcinoma (29 per cent), but is not as high as Lim *et al.* (88 per cent)[12].

Radiotherapy has been used in most series either as an adjuvant to surgery or as the sole form of therapy[16]. The case for adjuvant radiotherapy remains unproven by any single study since small numbers mitigate against statistical proof of the almost universal improvement in survival found with radiotherapy[14–17]. Studies by Blackledge *et al.*[18] and Dworkin *et al.*[11] are exceptions to this. Our data support this but again fail to prove the case for using adjuvant radiotherapy. Herrmann *et al.*'s[16] argument that radiotherapy is as effective as surgery in early disease is unsubstantiated.

The role of chemotherapy cannot be assessed from our data.

A recent review by Perrin and Blackledge[1] reports rather disappointing response rates in advanced gastrointestinal lymphoma compared with those seen in nodal disease.

This series suggests that surgery is the treatment of choice for gastric lymphomas. Additionally the results of radiotherapy are sufficiently interesting to warrant a trial as an adjuvant to surgery. Chemotherapy should be evaluated in more advanced disease to determine its place. All trials must be stratified for stage as this is the most important prognostic factor.

Acknowledgements

We are grateful for the help of consultant pathologists and their staff from the following hospitals, for the provision of histology specimens: Birmingham General, Bromsgrove, Coventry and Warwick, Derby, East Birmingham, Queen Elizabeth, Royal Salop, Sandwell, Selly Oak, Walsgrave, Warwick, Wolverhampton, Worcester. We are also grateful to Vanessa Chadderton, Chris McConkey and Jan Robertson for their excellent technical assistance. The survey was supported by grants from the Medical Research Council and the Cancer Research Campaign.

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Paper accepted 25 January 1987

Br. J. Surg. 1987, Vol. 74, June,
488–490

Nissen fundoplication and pyloroplasty in the management of gastro-oesophageal reflux in children

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A retrospective study was carried out of children undergoing Nissen fundoplication and pyloroplasty for the correction of gastro-oesophageal reflux. Twenty children (thirteen males, seven females) aged 8 months to 12 years underwent surgery over a 10 year period. Forty per cent were mentally retarded. Presentation was failure to thrive in 19 (95 per cent), recurrent vomiting in 18 (90 per cent) and haematemesis in 14 (70 per cent). Four children had Barrett's oesophagus. There were no operative or perioperative mortalities. Follow-up (mean period 3 years, 9 months) revealed no further symptoms of reflux. The 'normal' children gained weight postoperatively whereas the 'retarded' group did not. Adhesion obstruction (10 per cent) was the major late postoperative complication. Regression of Barrett's epithelium was noted endoscopically. 'Gas-bloat' syndrome, a major complication following fundoplication, was not encountered.

Keywords: Gastro-oesophageal reflux, fundoplication, pyloroplasty

Medical management in the form of feed thickening, postural therapy and antacids is the mainstay of treatment of gastro-oesophageal reflux with or without hiatus hernia in infants and children[1–4]. The indication for surgery is recurrent vomiting and failure to thrive despite intensive medical measures. Haematemesis and respiratory problems are often associated[5]. The Nissen fundoplication is established as an effective method of preventing reflux[6]. It has been suggested that combining fundoplication with pyloroplasty may prevent a major cause of morbidity—the 'gas-bloat' syndrome[7,8]. Using failure of full medical therapy as indication for surgery 20 children had a Nissen fundoplication and pyloroplasty carried out over a 10 year period. The results of this procedure are reviewed.

Patients and methods

Over a 10 year period 1976–1986 20 patients were accepted for surgical correction of gastro-oesophageal reflux. Their age at time of surgery ranged from 8 months to 12 years (mean 4 years 8 months). Thirteen were male and seven female. The principal presenting symptoms were failure to thrive (95 per cent), recurrent vomiting (90 per cent) and haematemesis (70 per cent) (*Table 1*). The duration of symptoms ranged from 1 month to 11 years (mean 2 years 11 months). Twelve (60 per cent) had been symptomatic since birth. Eight of the twenty children (40 per cent) were mentally retarded with gross neuromuscular incoordination. Pre-operative investigations included a barium swallow in 19 (95 per cent) and oesophagogastroduodenoscopy in 17 (85 per cent). Gastro-oesophageal reflux was demonstrated in 18 of the 19 barium examinations, associated with a sliding hiatus hernia in 12. The findings at oesophagoscopy are listed in *Table 2*. Follow-up information on the 20 children was obtained either at the outpatient clinic or by personal communication with the parents. The follow-up ranged from 3 months to 10 years (mean 3 years 9 months). Specific enquiries were made as to postoperative weight gain, dysphagia, haematemesis, and the ability to burp and vomit.

Operative procedure

Operative procedure was based on the Nissen fundoplication in all children[6]. Nineteen procedures were carried out by an abdominal approach alone; in one a thoracoabdominal approach was utilized. The vagal nerves were preserved unless mobilization at the oesophagogastric junction was inhibited. In all cases a Heineke–Mikulicz pyloroplasty was carried out.

Results

There were no operative or perioperative mortalities and no major complications in the immediate postoperative period in either the 'normal' or the 'retarded' group of children. Three of the retarded group had minor postoperative complications. These comprised a prolonged ileus in two which resolved spontaneously and apnoeic spells in a third. The latter was found to be opiate related. All 20 children were asymptomatic on discharge from hospital.

Follow-up

Of the 12 'normal' children only one, thought to have the Rubenstein–Taybi syndrome, has not gained weight. Weight gain is shown in *Figure 1*. Nine have had no further problems. Revisional surgery has been required in one child, a second

Table 1 *Indications for surgery*

	Number*	Percentage
Failure to thrive	19	95
Recurrent vomiting	18	90
Haematemesis	14	70
Anaemia	7	35
Recurrent respiratory infections	3	15

* Total = 20

Table 2 *Findings at oesophagoscopy*

	Number*	Percentage
Distal oesophagitis	16	94
Hiatus hernia	11	65
Oesophageal ulceration	10	59
Barrett's oesophagus	4	24
Oesophageal stricture	3	18
TOFR stricture†	1	6

* Total number of endoscopies = 17
† Tracheo-oesophageal fistula resection

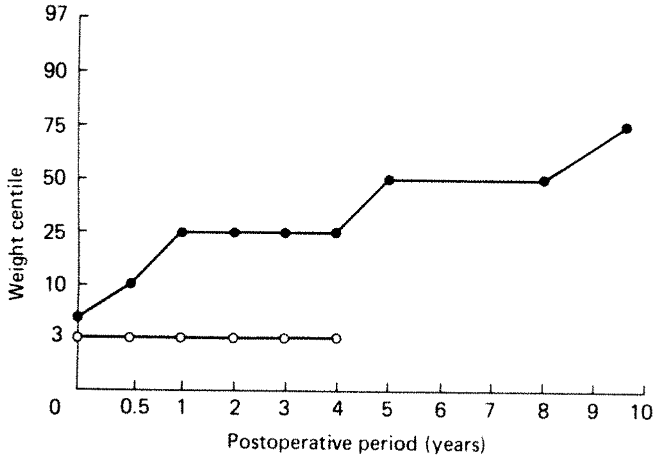

Figure 1 *Mean postoperative weight gain.* ●, *Normal children*;○, *mentally retarded children*

laparotomy for adhesion obstruction in another and a third died from peritonitis following volvulus of a small bowel loop.

All eight children with cerebral palsy had symptomatic improvement from surgery, but only one has shown significant weight gain. One child occasionally vomits and another is unable to burp but has no abdominal distension. Two children continue to have swallowing difficulties that were present pre-operatively. Adhesional small bowel obstruction has necessitated laparotomy in one child and another has died from pneumonia secondary to a progressive neurodegenerative disorder.

Two of the four children diagnosed pre-operatively as having Barrett's oesophagus have had repeat oesophagoscopy and show histologically proven regression of Barrett's epithelium.

Of the three children with oesophageal strictures pre-operatively only one has required dilatation on one occasion.

Discussion

The patients in this series represent the surgical management of gastro-oesophageal reflux in a region with a catchment area of 1·2 million over a 10 year period. At the Leicester Royal Infirmary one hundred contrast studies are done annually in children with symptoms suggestive of reflux. Confirmation is obtained in 20 per cent. About 10 per cent of this select group are considered for surgery.

The success of conservative measures such as postural therapy, feed thickening and antacids would suggest that surgery should be reserved for children who fail to respond to these measures. Reflux is common in infants and children and is often present in children with respiratory and/or feeding difficulties. In this series the accompaniment of these problems with reflux has not been used as indications for surgery unless endoscopic evidence of oesophagitis, ulceration or stricturing is present. This is at variance with other series[9,10].

Although many alternatives exist the Nissen fundoplication remains the operation of choice in most centres. The main criticism of this procedure is that complete invagination of the oesophagogastric junction may impede burping and vomiting and lead to the painful abdominal distension of the gas-bloat syndrome. Morbidity rates of 25–50 per cent have been reported[8]. In the present series this problem has not arisen. Similarly the problem has not been encountered in other series where fundoplication has been combined with pyloroplasty[7]. Gastric antral dyskinesia has been reported as accompanying reflux in 50 per cent of children and may be an important factor in the gas-bloat syndrome[11].

There was a high proportion of mentally retarded children in this series (40 per cent). Gastro-oesophageal reflux is becoming increasingly recognized as a major problem in severely retarded children many of whom have abnormal peristalsis and reduced basal lower oesophageal sphincter pressure[12]. Conventional medical therapy is less effective in these children[13]. Although weight gain is minimal following fundoplication, symptomatic improvement is marked.

Barrett's oesophagus, considered to have malignant potential and be secondary to severe reflux, was found endoscopically in four children pre-operatively (three male/one female)[14]. It has not previously been reported in a female under 10 years[15]. Whether it regresses following fundoplication is controversial[16]. Two children had repeat endoscopy. Complete resolution had occurred in one child and regression in the other. It may require considerable time for the transition from Barrett's to normal epithelium.

Late postoperative complications are common following Nissen's fundoplication. Most commonly reported are failures of operative repair, para-oesophageal herniae and adhesion obstruction[17-20]. Fundoplication appears to predispose to the development of band adhesions. Two (10 per cent) of this series required surgery for adhesions. In the Leicester area in 1983 and 1984, 950 abdominal operations were carried out in the under 15 years age group. Over this period only five children required surgery for adhesion obstruction.

Nissen fundoplication is an effective method of preventing gastro-oesophageal reflux in children. Combining the procedure with pyloroplasty appears to be effective in preventing a major problem—the 'gas-bloat' syndrome. Adhesion obstruction seems to be particularly prevalent following fundoplication. The significant incidence of late postoperative complications should prohibit its used in infants unless full medical therapy has failed and significant oesophageal disease has been established endoscopically. Barrett's oesophagus is of concern in view of its neoplastic potential. It has regressed following fundoplication in the cases undergoing repeat endoscopy. The mentally retarded symptomatically improve but show poor weight gain.

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Paper accepted 6 January 1987

Case report

Br. J. Surg. 1987, Vol. 74, June, 490

Gastric complication of massive Slow-K overdose

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The side effects of therapeutic doses of potassium supplements are well recognized and include oesophageal stenosis and gastric ulceration[1,2]. Reports of slow-release potassium supplements taken in overdose emphasize the immediate cardiotoxicity of the drug. We report a case in which the patient was successfully resuscitated but suffered a late complication which to our knowledge has not been previously reported.

Case report

A 50-year-old man presented having taken 160 Slow-K tablets 5 h previously. His pulse rate was 88 per min and blood pressure 100/60 mmHg. Physical examination was otherwise unremarkable. Initial investigations revealed a plasma potassium of 9·1 mmol/l and marked metabolic acidosis. Urea and sodium were normal. An electrocardiograph showed widening of the QRS complexes and tall peaked T waves.

He was given intravenous calcium chloride, insulin and dextrose, oral calcium resonium and lactulose, and intravenous fluids and frusemide to force a diuresis; he was commenced on peritoneal dialysis. When his condition was stable a gastric washout recovered numerous white tablets and tablet debris.

Despite these measures the plasma potassium was 8·9 mmol/l 7 h after admission but by 16 h it was 4·9 mmol/l. After recovering from the acute effects of the overdose the patient was discharged to psychiatric care. He was readmitted 12 weeks later with weight loss and vomiting.

Gastroscopy showed erosive gastritis. The stomach did not dilate with insufflation. A barium meal (*Figure 1*) showed a grossly contracted stomach with pseudodiverticula along the greater curve and deformity of the antrum. There was delay in gastric emptying. The patient underwent total gastrectomy 16 weeks after the overdose. Microscopic sections from the lesser curve showed scarring involving all layers of the stomach wall. There was evidence of a foreign body giant cell reaction in the serosa but the eliciting material was not identified.

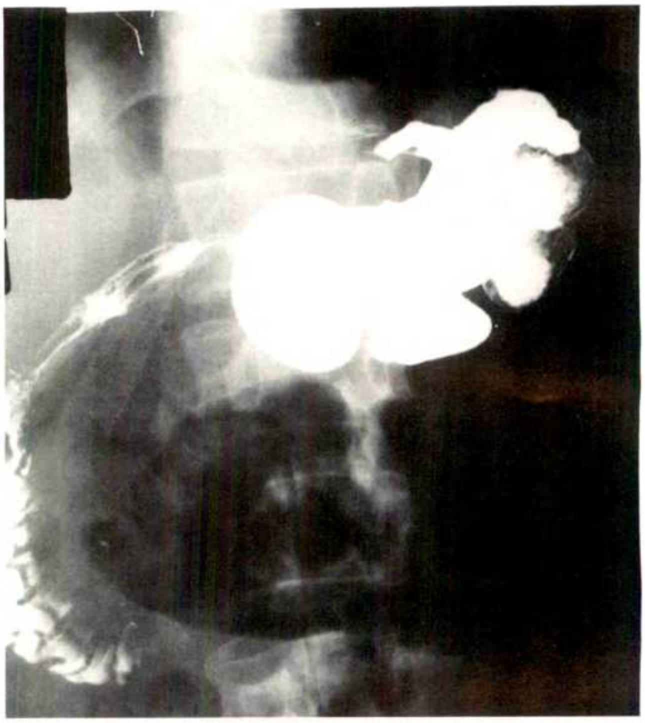

Figure 1 *Barium meal performed 12 weeks after initial presentation, following readmission with a history of vomiting and weight loss*

Discussion

Slow-K is the most widely prescribed potassium supplement and has been marketed in Great Britain since 1965. The slow-release formulation is designed to avoid high localized concentrations of potassium chloride which might damage the mucosa but these lesions continue to be reported.

The present case illustrates that attention to drug elimination in the management of Slow-K overdosage is important not only in aiding the initial management of the hyperkalaemia but also in preventing this significant late complication of severe gastric scarring following extensive mucosal erosion. A chest X-ray taken after gastric washout showed numerous residual tablets in the fundus of the stomach and it is presumed that they adhered to the mucosa despite lavage. A similar problem has been reported with slow-release theophylline[3]. In the case of overdose with Slow-K tablets, early gastroscopy should be considered to facilitate the removal of the tablets and if this is not sufficient, gastrotomy should be considered.

Acknowledgements

We thank Dr T. Northfield and Mr J. Kirkham for permission to report this patient under their case.

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Paper accepted 1 December 1986

Br. J. Surg. 1987, Vol. 74, June,
491–492

Effect of Roux-en-Y reconstruction on the gastric emptying of a solid meal

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The gastric emptying of a solid meal was measured in 39 patients after Roux-en-Y reconstruction and compared with that in 27 patients after truncal vagotomy and pyloroplasty and that in 22 patients after Polya gastrectomy. There were no significant differences among the groups. It is concluded that despite the disruption of the normal motor pathway produced by the Roux-en-Y reconstruction it does not lead to clinically significant delay in gastric emptying.

Keywords: Roux-en-Y, gastric emptying

The Roux-en-Y reconstruction is an effective operation for diverting duodenal contents from the stomach or oesophagus provided that the diverting loop is of adequate length (at least 40 cm)[1]. Unfortunately, not all patients who undergo Roux-en-Y reconstruction are cured of all their symptoms, even though duodenal contents can be shown to have been eliminated from the stomach. This can be due to poor selection of patients by inclusion of those whose symptoms are not due to enterogastric reflux.

The diagnosis of 'alkaline reflux gastritis' is notoriously difficult to substantiate and gastrointestinal motility disorders or psychiatric illness may be responsible for the patients' complaints. Furthermore, it has been suggested that the Roux-en-Y reconstruction itself may produce retardation of gastric emptying. It has been shown that the fasting migrating motor complex is absent or severely disrupted as the Roux limb is isolated from the small bowel pacemaker, situated in the duodenum[2]. In addition, when a Polya partial gastrectomy precedes the Roux-en-Y reconstruction it is usual practice to perform a truncal vagotomy to reduce the risk of stomal ulceration. Such patients may develop gastric retention due to the gastric atony which follows vagotomy.

To evaluate these factors we measured the gastric emptying of a solid meal in patients who have had a Roux-en-Y diversion for symptoms of alkaline reflux and compared them with patients who have had a Polya partial gastrectomy or truncal vagotomy and pyloroplasty (TV + P) for duodenal ulcer disease.

Patients and methods

Between 1980 and 1985, 39 patients had a Roux-en-Y- diversion for symptoms of enterogastric reflux, the occurrence of which had been confirmed by HIDA scanning[3]. Those patients who had a Roux-en-Y after partial gastrectomy ($n = 14$) had a truncal vagotomy performed at the time of the diversion. Nine patients had already had a truncal vagotomy and antrectomy. The 16 patients who had a diversion after vagotomy and pyloroplasty had an antrectomy performed at the time of the diversion. The gastric emptying of a solid meal was studied and compared with that in 27 patients who had a vagotomy and pyloroplasty and 22 patients who had a Polya gastrectomy for duodenal ulcer disease. None of these patients has subsequently required surgical reconstruction for symptomatic side-effects from their gastric operation. Of the 39 Roux patients, 7 had their gastric emptying study within 1 year of the operation. All the Polya and TV + P patients were studied at least 5 years after operation.

The gastic emptying of a 400 ml meal (minced meat, peas, potatoes and milk) was measured for 70 min in the sitting position using a gamma camera. The meal was labelled with a 4 MBq ^{113}In, which was cooked with the meal. This has been shown to distribute the radiolabel throughout the many particle sizes of the meal[4].

Gastric emptying studies have been interpreted by calculating the best fit exponential regression of the gastric counts from the peak count onwards. The $t_{\frac{1}{2}}$ of this regression has been used as an easily comprehensible index of the regression analysis. The Mann–Whitney *U* test has been used to compare the data which are non-Gaussian in distribution.

Results

The median $t_{\frac{1}{2}}$ in the Roux-en-Y patients was 51 min (range 2–400 min), in the Polya patients median $t_{\frac{1}{2}}$ was 45 min (range 2–323 min) and in the TV + P group the median $t_{\frac{1}{2}}$ was 48 min (range 12–458 min) (*Figure 1*). There were no significant differences among the three groups of patients.

The upper limit of our normal range[5] is 81 min. Eight of the Roux patients (21 per cent), five of the Polya patients (23 per cent), and five of the TV + P patients (19 per cent) had a $t_{\frac{1}{2}}$ longer than 81 min.

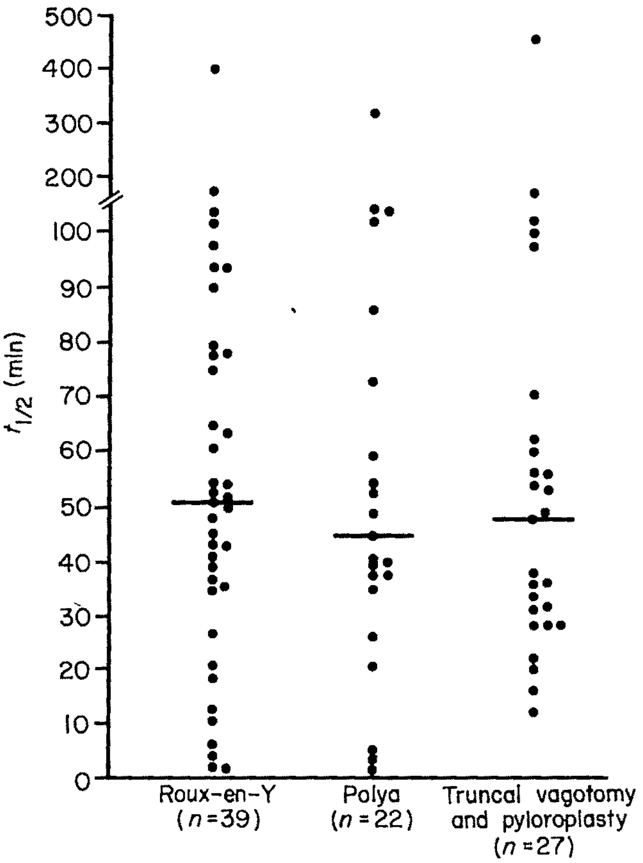

Figure 1 *Solid meal gastric emptying results*

Discussion

Unfortunately our study did not start until 1985, consequently we have not studied gastric emptying prospectively before and after Roux-en-Y diversion. However, there is no evidence from our data that the Roux-en-Y reconstruction is more likely to cause delayed gastric emptying than either Polya gastrectomy or TV + P. Seven patients in the Roux-en-Y group were studied within 1 year of their operation when delayed gastric emptying is more common. Apart from the overall similarity of the results there is no increase in the proportion of patients with half-lives above the upper limit of our normal range when symptoms of gastric retention may occur. Only two patients after Roux-en-Y had severe symptoms from gastric retention (that is, pain and food vomiting). Both had stenosed stomata on endoscopic examination without evidence of peptic ulceration and both were cured of their symptoms by surgical revision of the stoma. Only one of these patients had gastric emptying measurements before and after the revisional procedure which reduced the $t_{\frac{1}{2}}$ from 263 to 121 min.

We conclude that the disturbances of normal motility recorded by intraluminal pressure measurements after Roux-en-Y reconstruction[2] are not significant factors in the production of clinical disease. In performing the operation it is, however, important to ensure that the stoma created between the stomach and the jejunum is fashioned at the dependent lower border of the stomach and makes use of the whole of the diameter of the small bowel. This may be facilitated by the use of stapling instruments.

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Paper accepted 28 December 1986

Br. J. Surg. 1987, Vol 74, June,
493–495

Digital ischaemia and palpable pedal pulses

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Digital ischaemia in the presence of an otherwise well-perfused foot in the non-diabetic patient presents diagnostic problems especially as the manifestations are frequently evanescent. Eighty such patients (sixty men and twenty women aged 55–84 years) who presented to St. Laurence's Hospital from 1982 to 1985 inclusive were evaluated. Micro-embolization was inferred from the demonstration of a cardiac (20) or an arterial source (42) in 62 of 80 patients. In 14 of the remaining 18 patients a malignancy was diagnosed, which was found to be visceral cancer in 11 cases. Indium platelet scanning revealed platelet aggregation in 14 of 26 patients examined. Laboratory evidence of abnormalities of platelet aggregation or blood coagulation was found in only 6 patients. There have been no further symptoms in 37 patients who have been treated surgically or in 17 of 21 patients who have been treated with either anticoagulation or antiplatelet therapy.

Keywords: Digital ischaemia, microemboli, arterial plaque, aneurysm, arrhythmia

The 'blue toe' syndrome, i.e. digital ischaemia in the presence of palpable pedal pulses is recognized as arising from upstream arterial lesions such as aneurysms and atheromatous plaques[1,2]. However, the evanescent nature of the clinical manifestations and the reported response to antiplatelet therapy has tended to underplay the significance of the syndrome[3]. It is important to be aware that the condition is often a harbinger of other significant pathological processes. We have therefore analysed the aetiological factors involved in 80 consecutive non-diabetic patients who presented with the 'blue toe syndrome' to the Vascular Department at St. Laurence's Hospital, Dublin, over the period January 1982–December 1985.

Patients and methods

Eighty such patients (sixty men and twenty women aged 55–84 years) were evaluated by a combination of physical examination, haematology, coagulation screening, platelet aggregation studies, indium platelet scanning, angiography, ultrasound and cardiac assessment. Coagulation screening included platelet count, prothrombin time and partial thromboplastin time. Platelet aggregation studies and indium platelet scanning were performed in 26 patients. Ultrasound examination of the aorta was performed in all patients and biplanar angiography in those in whom ultrasound and cardiac assessment were normal and in whom only unilateral digital ischaemia was present. Since all patients had at least one palpable pedal pulse in the affected limb Doppler pressures were not routinely performed.

Results

Arterial lesions

Micro-embolization was inferred from the finding of an arterial lesion in 42 patients (*Table 1*). There were 18 aneurysms: 3 popliteal and the remainder either aortic or iliac. In 24 patients a plaque or a stenosis was found at angiography in the aorta (6), iliac (3), femoral (8) and popliteal arteries (7). In 29 of 42 patients the arterial lesion was initially diagnosed clinically. There were no further symptoms or digital loss in 37 patients treated surgically. These included five patients treated initially by anticoagulation or antiplatelet therapy, in three of whom the arterial lesion progressed to occlusion. Four patients with diffuse arterial lesions remain asymptomatic on antiplatelet therapy. In one patient with a popliteal aneurysm anticoagulation was stopped because of acute pancreatitis. The aneurysm thrombosed with resultant limb loss.

Indium platelet scintigraphy was performed in 26 patients and in 14 of 19 proven arterial lesions localized platelet aggregation was demonstrated. These arterial lesions included both aneurysms and plaques and in the five false negative patients (two aneurysms, three plaques) organized thrombus was subsequently found at operation.

Cardiac abnormalities

In 20 patients in whom ultrasound examination of the proximal arterial tree was clear, micro-embolization was inferred from the finding of a cardiac abnormality (*Table 2*). The majority of these had bilateral symptoms but in three patients with a diagnosis of endocarditis which was subsequently confirmed by blood cultures, echocardiography and in one case at autopsy the digital symptoms were unilateral. In two patients a valvular abnormality was found, in one of whom mitral valve prolapse was diagnosed only after echocardiography. In five of fifteen patients with a cardiac arrhythmia the diagnosis was only established after prolonged electrocardiographic monitoring. Intermittent or persistent atrial fibrillation was found in 12 of these 15 patients.

Three patients with digital micro-embolization from a cardiac source had a major cerebrovascular ischaemic episode shortly after presentation, one of whom died of a massive cerebral

Table 1 *Distribution of arterial lesions in 42 patients with arterial source of micro-emboli*

Aneurysms		Plaque/stenosis	
Site	No.	Site	No.
Aortic	14	Aortic	6
Popliteal	1	Iliac	3
Iliac	3	Femoral	8
		Popliteal	7

Table 2 *Abnormalities identified in 20 patients with cardiac source of micro-emboli*

Abnormality	No.
Arrhythmia	15 (occult in 5)
Endocarditis	3
Valvular disease	2

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Table 3 *Malignancies identified in 14 patients with digital ischaemia due to microthrombosis*

Tumour	No.
Adenocarcinoma	8
Reticuloses	3
Squamous	2
Undifferentiated	1

infarction. Three of the seventeen patients treated by systemic anticoagulation required the addition of antiplatelet agents to control symptoms and one patient required a minor toe amputation. One patient died from complications of bacterial endocarditis.

Malignancy

In 14 patients an underlying malignant process was discovered. There were three reticuloses and in the remainder a solid visceral cancer was found (*Table 3*). Of these 11 cancers 8 were adenocarcinomas. The primary sites were colon (3), prostate (2), small bowel (1), stomach (1) and pancreas (1). The majority had an advanced tumour with distant metastases but in two patients the digital ischaemia was present for some months prior to the discovery of the underlying cancer.

Abnormal coagulation or platelet aggregation

Laboratory evidence of abnormal coagulation or platelet aggregation was uncommon. In only one was increased platelet aggregation detected even though indium scintigraphy revealed localized platelet aggregation in 14 patients with arterial lesions and in a further patient who later proved to have metastatic malignancy of unknown origin. In the remaining five there was one case each of macroglobulinaemia, thrombocytosis and disseminated intravascular coagulation and two cases of primary polycythaemia. Both patients with polycythaemia ultimately required major limb amputations. Four of the six haematological abnormalities were in patients with cancer.

Discussion

The natural history of digital ischaemia secondary to an arterial lesion is either limb loss from a major embolus or an acute-on-chronic arterial occlusion or substantial risk to life from the complications of aortic and other aneurysms[1]. Thus, in the management of a patient with a suspected arterial lesion the priority must be the identification of either aneurysmal disease or lesions with superimposed thrombotic material which are then dealt with on their own merits. Vascular reconstruction

[redacted]

therapy for those patients in whom there are multiple arterial lesions and/or in whom the risks of arterial reconstruction are prohibitive. Here platelet scintigraphy, notwithstanding its lack of sensitivity, may identify those lesions likely to be symptomatically controlled by aspirin and other antiplatelet drugs[5].

Not only must the arterial tree in patients with obvious digital ischaemia be fully evaluated but 'at risk' patients must be identified. These patients often have very subtle symptoms the importance of which is only recognized after the event. Certainly, analysis of these patients suggests that intermittent paraesthesiae, vague calf pains and 'ingrown toe-nail' should be regarded as possible ischaemic manifestations and investigated appropriately. It is also clear that many patients with occlusive arterial lesions have physical signs highly suggestive of pre-occlusive micro-embolization[6].

In 17 patients with bilateral pedal ischaemia and no arterial lesion detected on investigation the heart was presumed to be the source of the micro-emboli. In a further three patients with unilateral digital ischaemia subacute bacterial endocarditis was later diagnosed. In only two patients was there evidence of intracardiac thrombosis on echocardiography[7]. The cardiac anomalies were initially occult in the majority of patients. Subtle presentations of both valvular heart disease and bacterial endocarditis are a feature of modern cardiac practice and are not entirely unexpected. On the other hand an intermittent arrhythmia was detected more frequently than might have been anticipated from previous experience with major peripheral emboli. It can however readily be appreciated how forceful atrial contraction following on the restoration of sinus rhythm would favour the embolization of thrombi formed in the stagnant blood of the fibrillating atrium. The mildness of clinical presentation was not matched by the clinical course in these cardiac patients. One patient died of complications of endocarditis; a further three patients experienced major cerebrovascular ischaemic episodes which proved fatal in one. Thus patients with a suspected cardiac source should be vigorously investigated as an emergency and treated appropriately with either systemic antibiotics or anti-coagulation. The identification of occult arrhythmias in 5 of 20 patients undergoing Holter monitoring suggests that if we had performed this examination in all 80 patients we may have demonstrated more than one potential source of emboli in some patients. However, in instances where we identified a proximal arterial source in patients with bilateral symptoms we inferred that to be the source. Presently our policy would be to perform cardiac and arterial assessment in all patients with blue toes.

Microthrombosis in association with malignant disease is just one of the many expressions of a generalized disturbance of intravascular coagulation of which migratory thrombophlebitis

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Paper accepted 30 December 1986

Announcement

Reviews

The Editorial Board of *The British Journal of Surgery* continues to invite review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium of £100. Potential authors seeking advice on the suitability of review topics are advised to contact: Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Glasgow G31 2EU, UK.

Leading articles

The Editors invite submission of signed leading articles to *The British Journal of Surgery*. These articles should be 600–1000 words in length, should address controversial topics of current interest and should be supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium of £100 is payable on publication. Potential authors seeking advice on the suitability of topics are advised to contact: Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Glasgow G31 2EF, UK.

Surgical workshops

The Editors invite the submission of articles describing technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they can be accompanied by no more than two figures but should not carry supporting references. Articles submitted to the Surgical Workshop series may be subjected to external review and assessment by the Editorial Board before acceptance.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is likely to be high. Authors are advised to restrict such reports to a maximum of 500 words, to use no more than five references and to submit no more than one illustration.

Br. J. Surg. 1987, Vol 74, May, 496–499

Asymptomatic carotid murmur: ultrasonic factors influencing outcome

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Sixty consecutive patients with an asymptomatic mid-cervical murmur on auscultation were identified amongst 1000 patients who underwent duplex scanning of the extracranial carotid arteries during 1981–83. They were classified according to the scan results into 12 high risk subjects with >75 per cent stenosis of an internal carotid artery, 37 low risk subjects with a <75 per cent stenosis and 6 with no detectable stenosis. The mean duration of follow-up was 3 years (minimum 2 years) or until stroke or death. One was lost to follow-up and four were excluded having undergone carotid endarterectomy during the study. Six of twelve subjects with >75 per cent stenosis suffered a stroke (five fatal and one non-fatal). There were no premonitory signs except in one patient with non-focal cerebral ischaemia for 2 months before an hemispheric stroke. There was one fatal stroke in the <75 per cent stenosis group and none in the control group. In all, 17 (28 per cent) patients died (myocardial infarction, 8; stroke, 6; malignant disease, 3). These results confirm that asymptomatic carotid murmurs are associated with increased mortality with most having non-severe carotid disease on duplex scanning and few strokes during follow-up. There is an important minority with tight carotid stenosis who carry a worrying risk of stroke if left untreated.

Keywords: Carotid murmur, ultrasound, stroke, carotid endarterectomy

The management of asymptomatic carotid murmur is still controversial[1]. Two population-based epidemiological studies[2,3] have shown a poor correlation between carotid murmur and stroke. However, these studies provided no information on the underlying carotid pathology. Angiographic studies have shown that only about half of carotid murmurs are associated with >50 per cent stenosis of the internal carotid artery[4,5].

Some authors[6–8] feel that the risk of stroke is sufficiently high that prophylactic endarterectomy is justified. Others[9–11] suggest that carotid surgery can be safely delayed until symptoms develop.

The substantial variation in published results suggests that sub-groups may exist within the asymptomatic murmur population. This study attempts to shed some light on the natural history of this condition.

Patients and methods

Sixty consecutive patients with an asymptomatic mid-cervical murmur were identified amongst 1000 patients who underwent duplex scanning of the carotid arteries in the neck in the Vascular Studies Unit at Bristol Royal Infirmary between January 1981 and June 1983. Those who had previously undergone a carotid endarterectomy were excluded. There were 41 men and 19 women, with a mean age of 61 years. Mean follow-up was 36 months, range 24–55 months.

There were 29 patients who had been referred from peripheral vascular clinics and 16 of them had had an arterial operation at another site; 23 patients had been treated for hypertension, 9 for diabetes mellitus and 20 patients had angina or myocardial infarction. Amongst them, 7 patients had undergone coronary artery by-pass grafts, 42 patients were cigarette smokers and 26 patients were on regular aspirin treatment in a dose ranging from 300 to 1200 mg/day.

All underwent a detailed clinical assessment including auscultation of the precordium, supraclavicular fossae and the neck by two independent observers.

For all patients who died during the follow-up period, the cause of death was established from the death certificate, hospital notes or autopsy report if carried out.

Duplex scanning

Carotid scanning was carried out using a Mark 500 ATL (Advanced Technology Laboratories, Squibb Medical Systems) duplex scanner, which combines real-time B-mode imaging with a pulsed Doppler flowmeter. The B-mode image was used to identify the carotid arteries and visualize plaques, to place the sample volume of the pulsed Doppler in the centre stream of the vessel and to measure the angle of insonation. A Doppler angle of approximately 60° provided a favourable return signal. In addition to the audible interpretation, the Doppler signals were sent to an on-line real-time spectral analyser. The image and Doppler information from common, internal and external carotid arteries were recorded on videotape for later review and further processing of the velocity signal. Hard copy output of the spectral analysis was obtained on light sensitive paper in the form of frequency against time waveforms with the amplitudes of back-scattered signal expressed in levels of grey.

Disease of the internal carotid artery was classified into five categories according to imaging of atheromatous plaque, spectral broadening, peak systolic and maximal diastolic frequency: normal—no plaque, no spectral broadening and systolic peak frequency up to 4 kHz; <50 per cent diameter stenosis—atheromatous plaque, spectral broadening and systolic peak frequency up to 4 kHz; 50–75 per cent diameter stenosis–atheromatous plaque, spectral broadening throughout systole, systolic peak frequency >4 kHz with increased diastolic frequency; >75 per cent diameter stenosis—atheromatous plaque, systolic peak frequency >7·5 kHz and diastolic frequency >4 kHz; occlusion—absence of signal in the internal carotid artery, low diastolic flow in the common and enhanced flow in the external carotid artery.

During the same period 90 patients had tri-plane carotid angiography including 7 patients from this study; duplex scanning was compared with angiography and for stenoses >50 per cent, the sensitivity was 97 per cent and specificity was 92 per cent.

Subjects with asymptomatic carotid murmurs were divided into three groups according to the ultrasonic severity of disease in the internal carotid artery regardless of the side of carotid murmur, because murmurs can arise from augmented flow in the normal contralateral side of an occluded internal carotid artery. The groups were as follows: normal, i.e. no stenosis detectable by duplex scanning; <75 per cent stenosis; and >75 per cent stenosis or occlusion of the internal carotid artery.

Table 1 *Classification of patients according to the severity of internal carotid artery stenosis*

Stenosis	Mean age (range)	Men:women	Total
0	59 (18–67)	3:3	6
<75 per cent	61 (33–82)	25:12	37
>75 per cent	64 (45–81)	9:3	12

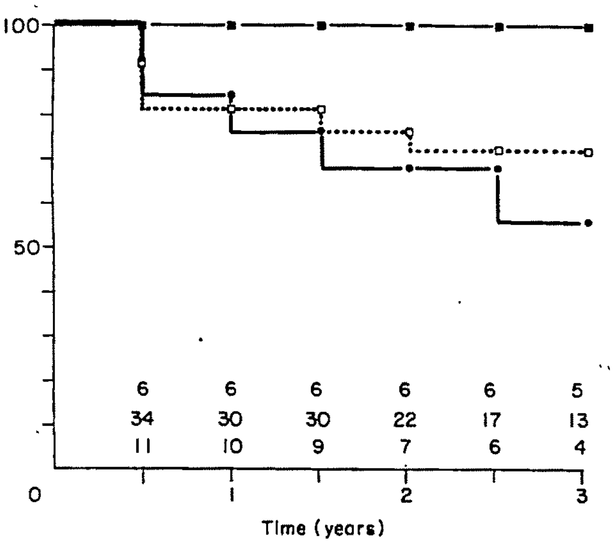

Figure 1 *Life table analysis of survival by severity of carotid stenosis, showing numbers of patients entering each follow-up interval:* ■, *no stenosis;* □, *<75 per cent stenosis;* ●, *>75 per cent stenosis and occlusion; for* □ versus ● P *n.s.*

Five patients were later excluded from the study. One was lost to follow-up and four underwent subsequent carotid endarterectomy (two had simultaneous carotid endarterectomy and coronary artery by-pass grafts, one patient had >90 per cent stenosis in both sides in whom bilateral carotid endarterectomies were performed and the remaining patient had >90 per cent stenosis in the operated side and occlusion in the opposite side). All four patients were asymptomatic before and after the operations, with a widely patent artery at latest follow-up.

Results

Seventeen patients (28 per cent) died during follow-up. The causes of death were myocardial infarction in eight, stroke in six and malignancy in three (two carcinoma of bronchus and one carcinoma of colon). In respect of general risk factors, there was an increase in age and a preponderance of males with increasing severity of stenosis. No differences were detected in other risk factors, including hypertension, coronary artery disease and diabetes.

Subjects with no disease detectable by duplex scanning

There were six subjects in this group, three men and three women (mean age 59) (*Table 1*). Three were hypertensive. At follow up, all were symptom free. The aetiology of murmur in three was as follows: venous hum, A–V malformation and physiological in an 18-year-old man. The murmur disappeared in two patients who were under treatment for hypertension.

Subjects with <75 per cent stenosis of an internal carotid artery

There were 37 subjects, 25 men and 12 women, with a mean age of 61 years (range 33–82) (*Table 1*). Twelve were hypertensive. Eleven (30 per cent) died during the follow-up, seven from myocardial infarction, three from malignancy and one from stroke after she had become symptomatic for 2 months (*Figures 1* and *2*). Three patients developed symptoms (1 amaurosis fugax, 2 vertebrobasilar). The severity of carotid stenosis increased to 75 per cent in three asymptomatic subjects.

A murmur arose from external carotid stenosis in seven patients in whom the ipsilateral internal carotid artery was <50 per cent stenosed.

In addition to the mid-cervical murmur, a subclavian murmur was detected in seven patients, indicating proximal atheroma of the main aortic arch branches.

Subjects with >75 per cent stenosis or occlusion of an internal carotid artery

There were 12 subjects, 9 men and 3 women, with a mean age of 64 years (range 45–81) (*Table 1*). Five were hypertensive. Ten (83 per cent) were smokers and on aspirin treatment, seven had a prior peripheral vascular operation and four had a previous myocardial infarction.

Six patients (50 per cent) died during the follow up period, five from stroke and one from myocardial infarction (*Figures 1* and *2*). There were no premonitory signs before the strokes. One had a non-fatal stroke, giving a total stroke rate of 50 per cent. This patient had non-focal cerebral ischaemia for 3 months before an hemispheric stroke. Two other patients developed non-focal symptoms (vertebrobasilar and subclavian steal) during the study. No ultrasonic progression of disease was noted in this group.

Carotid endarterectomy

During the period of this study, we performed 72 carotid endarterectomies on 68 patients. All except four were for TIAs and/or amaurosis fugax and 49 had >75 per cent carotid stenosis. They were otherwise similar to the asymptomatic murmur group in terms of age, sex and prevalence of hypertension, coronary artery disease and diabetes.

The results were that three patients died from stroke during the early postoperative period (4·4 per cent). None developed a stroke during three monthly follow-up for up to 3 years. *Figure 3* shows a statistical difference in the stroke rate between the surgically treated and medically treated groups. Of course, treatment of these contemporary, non-identical groups was not selected at random, since surgery was preferred for those with more severe disease, i.e. transient ischaemia attacks (TIAs) plus tight carotid stenosis. Even so, the surgical group fared better than the non-intervention group.

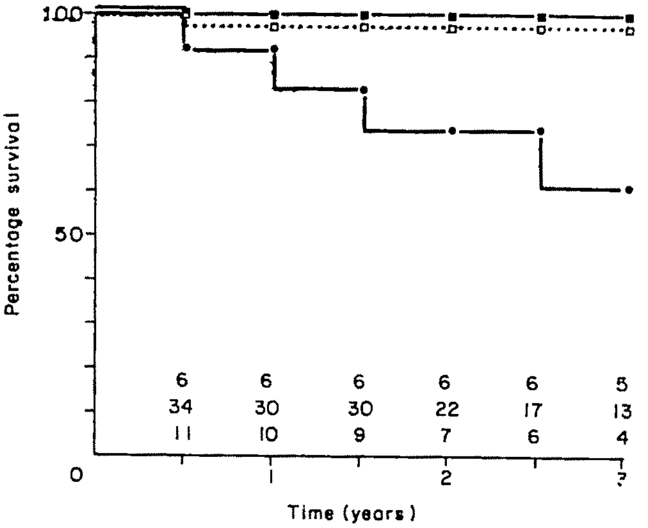

Figure 2 *Stroke mortality related to severity of carotid stenosis. Life table analysis showing numbers entering each follow-up interval:* ■, *no stenosis;* □, *<75 per cent stenosis;* ●, *>75 per cent stenosis and occlusion; for* □ versus ● P=*0·005*

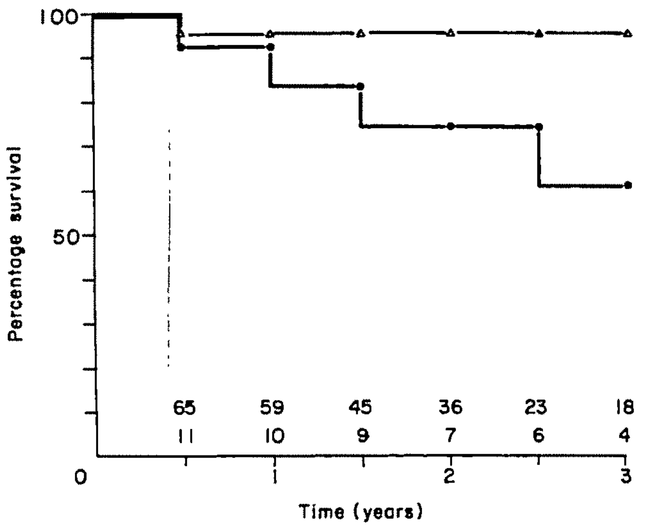

Figure 3 *Life table showing impact of stroke mortality on outcome of severe carotid stenosis .treated medically and surgically;* △, *endarterectomy;* ●, *>75 per cent stenosis, medically treated;* $P=0{\cdot}001$

Discussion

The prevalence of asymptomatic carotid murmur increases with age and affects 4 per cent of the general population above the age of 50 years[2,3]. According to angiographic studies about half of carotid murmurs have >50 per cent stenosis of the internal carotid artery[4,5]. With the increased efficacy of non-invasive tests in the evaluation of extracranial carotid artery disease[12], screening of asymptomatic carotid murmur patients has been recommended by many authors[6,13].

Difficulties can arise when non-invasive tests diagnose haemodynamically significant internal carotid artery disease. The core of the problem is that stroke can occur without warning. In the literature, the incidence of stroke without antecedent (TIAs) varies from 1–50 per cent[10,14]. Cooperman *et al.*[7], Dorazio *et al.*[8] and Thompson *et al.*[6] reported 15–18 per cent of stroke without antecedent TIAs and for this reason they recommended endarterectomy for those patients with a haemodynamically significant disease. A contrasting view is that presented by Greenhalgh and Rose[9], Humphries *et al.*[10] and Roederer *et al.*[11], who report 1–2 per cent of such strokes. These authors believe that carotid surgery can safely be delayed until symptoms of TIAs develop. Meanwhile they suggest regular follow-up by non-invasive tests and explanations of premonitory symptoms with advice to report any suspicion of TIAs without delay.

This substantial variation in reported outcome suggests that sub-groups exist within the population of asymptomatic murmur patients. Roederer *et al.*[11] conducted a prospective study with the duplex scanner to follow 162 patients with asymptomatic carotid artery murmur for 3 years. They found that patients with >80 per cent stenosis have a higher risk of TIA, stroke and occlusion than patients with <80 per cent stenosis. They found that while no spontaneous strokes occurred in the low risk group, the incidence was 12·5 per cent in patients with an 80–99 per cent stenosis. In our study, five of twelve patients (42 per cent) who had >75 per cent stenosis died by stroke without warning (*Figure 2*) and no patient with <75 per cent stenosis died of such stroke ($P=0{\cdot}002$, Fisher's exact test). Of course, our study was retrospective and it is difficult to be certain whether the strokes had been preceded by a TIA. Further, there is the possibility of inaccuracy of the death certificate in defining the cause of death[15].

Recently, clinicopathological studies of carotid atheroma harvested at carotid surgery have shown that intraplaque haemorrhage is found more frequently in symptomatic than asymptomatic plaques[16]. Lusby *et al.*[17] showed a higher incidence of recent intraplaque haemorrhage in symptomatic (92 per cent) than in asymptomatic patients (27 per cent).

Pre-operative studies of plaque morphology are feasible nowadays with the development of high resolution scanners. Reilly *et al.*[18] correlated ultrasound with histopathology and demonstrated that intraplaque haemorrhage can be identified pre-operatively. Two distinct ultrasound echo patterns were recognized: heterogenous echo patterns indicating intraplaque haemorrhage in 82 per cent and homogenous echo patterns indicating fibrous plaque containing collagen in 78 per cent.

In our study, 91 per cent of the plaques were homogenous dense fibrous plaques at initial study. One patient in the high risk group (i.e. >75 per cent stenosis) developed a non-fatal stroke and we were able to study him again. Comparison of the ultrasonic B-mode image before and after the stroke showed that plaque in the stroke side had changed from homogenous to a heterogenous appearance, indicating intraplaque haemorrhage leading to occlusion of the internal carotid artery.

More recently, Johnson *et al.*[19] showed that patients with >75 per cent area stenosis of soft plaques had a 19 per cent incidence of stroke, compared with 9·5 per cent for dense plaques and no strokes for calcified plaques in a study of 297 patients with asymptomatic carotid murmurs followed prospectively for 3 years using B-mode ultrasonography.

Fields in 1979[1] recommended aspirin treatment for patients with asymptomatic carotid murmur and indeed 83 per cent of our patients with >75 per cent stenosis were on aspirin treatment. Perhaps the wisdom of aspirin treatment in the high risk group (i.e. >75 per cent stenosis) should be reconsidered, since many authors have shown that intraplaque haemorrhage[16,17] is closely associated with the development of cerebrovascular symptoms from a sudden increase in stenosis or cerebral embolization[20].

In conclusion, asymptomatic carotid murmurs are associated with increased cardiac and malignant mortality during follow-up. Most have mild carotid disease on duplex scanning and have a good cerebral prognosis. There is an important minority with tight carotid stenosis who have a worrying risk of stroke if left untreated.

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Paper accepted 30 December 1986

Case report

Br. J. Surg. 1987, Vol. 74, June, 499

Ureteroduodenal fistula

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Entero-urinary fistulas are classified as being high or low. The former include reno-, pyelo- and uretero-enteric fistulas while the latter comprise vescico-enteric fistulas. Amongst the high fistulas the ureteroduodenal variety is rare.

Case report

A 48-year-old stone mason injured his left kidney falling from scaffolding. At operation a horse-shoe kidney was discovered and the left moiety excised. At this operation the right ureter was inadvertently divided and an end-to-end anastomosis was performed.

The postoperative course was complicated by ureterocutaneous and colocutaneous fistulas, for which a right nephropyelo-ureterostomy, a new uretero-ureterostomy and a right hemicolectomy were performed.

A nephrostogram subsequently showed a ureteroduodenal fistula and the patient was referred to us. At a further operation the ureteric end of the fistula was resected and the uretero-ureterostomy refashioned along with closure and inversion of the duodenal end of the fistula, and drainage.

A ureterocutaneous fistula remained for 2 months, after which it spontaneously closed and normal micturition was regained.

Renal failure followed subsequent infection with *Pseudomonas* but was successfully treated. Urography and renal scintigraphy were normal 1 year after the original accident and the patient remains clinically and biochemically well 6 years later.

Discussion

The formation of a ureteroduodenal fistula is very rare: only nine cases have been described in the literature[1–9]. The aetiology is varied and often merely presumed. Davis[1] and Deslesaver[2] claimed the cause was chronic urinary infection (in one case attributed to renal calculi). Other researchers have said that the aetiology was duodenal ulcer or perforated diverticula in the ureter. In our patient (as in two other cases[3,7]) the cause was iatrogenic.

The altered anatomy (horseshoe kidney) and the presence of a retroperitoneal haematoma may have contributed to the accidental severing of the right ureter during the first operation. The ureteroduodenal fistula may have formed because of concurrent infection or it may have been accidentally created by catheterization during nephropyeloureterostomy.

Clinically these fistulae all present uniformly as chronic or recurrent urinary infection. In three of these cases occasional pneumaturia was reported.

The management of uretero-duodenal fistula in patients with a functioning controlateral kidney consists of nephrectomy and nephro-ureterectomy, especially in the presence of serious pyelonephritic complications. An exception was made for the patient operated on by Shiozaki *et al.*[6] who performed only a fistulectomy.

In our patient the presence of a single kidney demanded conservative surgery.

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Paper accepted 12 December 1986

0007–1323/87/060499–01$3.00

Br. J. Surg. 1987, Vol. 74, June,
500–503

Treatment of mesenteric infarction

Eighty-one cases of mesenteric infarction documented by angiography, laparotomy or autopsy were reviewed to assess the cause of the persistently high mortality. Thirty-seven patients (46 per cent) were felt to have inoperable lesions and were treated by supportive care only, while forty-four (54 per cent) underwent bowel resection and/or revascularization. Of these 44 patients 20 (45 per cent) survived, 14 (32 per cent) died of an early recurrence of infarction and 10 (23 per cent) died of an unrelated cause. In view of the high recurrence rate in the early postoperative period, treatment must prevent the causes of persistent or recurrent ischaemia such as vasoconstriction and reperfusion tissue damage. On the basis of recent clinical and experimental research we suggest that treatment should include routine angiography with selective perfusion of vasodilators through the superior mesenteric artery, pharmacological prevention of ischaemic and reperfusion tissue damage before surgery, and postoperative anticoagulation.

Keywords: Mesenteric infarction, prognostic factors, early recurrent ischaemia, policy for management

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The management of patients with mesenteric infarction still presents a most challenging and controversial problem[1,2]. The condition affects old and seriously ill patients and the diagnosis is often delayed resulting in an overall mortality which exceeds 70 per cent. Persistently high mortality, despite successful revascularization or bowel resection indicates that other factors are involved in the fatal outcome[1,3–6]. Recent studies have highlighted the potential role of pre-operative angiography with selective injection of vasodilators into the superior mesenteric artery (SMA) allowing an early diagnosis and reversing the persistent vasoconstriction incriminated in all forms of infarction[6–14].

In a retrospective study we have reviewed all cases of mesenteric infarction treated at the Basle University Hospital between the years 1968 and 1984. Our standard management consisted of laparotomy and bowel resection and eventually revascularization, but did not include routine angiography. The purpose of this analysis was to unravel the causes of a persistently high mortality and to define a more effective form of management based on our results and recent clinical or laboratory findings.

Patients and methods

The case histories of 81 patients treated for mesenteric infarction at the University Hospital of Basle between 1968 and 1984 have been reviewed. The diagnosis was ascertained in all cases on the basis of angiography ($n=19$), laparotomy ($n=69$) and/or autopsy ($n=55$). The series included 44 women and 37 men. Their median age was 70·6 years (71·4 for the women and 69·2 for the men), with a range from 27 to 89 years.

Clinical presentation

All 81 patients presented with abdominal pain. Forty had diarrhoea and sixty had nausea or vomiting. The duration of abdominal pain before admission varied from 2 h to 22 days. Clinical signs of peritonitis—tenderness, rebound pain and guarding—were present on admission in 38 cases (47 per cent). The white cell count was available in 76 patients. It was $<10\,000/\text{mm}^3$ in eight cases (11 per cent), and > 15 000 in fifty-four cases (71 per cent) and > 30 000 in twelve cases (16 per cent). Serum amylase concentration was recorded in 47 patients and was elevated in 25 cases (53 per cent) but the elevation never exceeded twice the normal level. A history of cardiac disease was present in 67 patients (83 per cent). Cardiac arrhythmia was noted in 51 patients (63 per cent) and symptomatic cardiac failure, treated or not, in 39 patients (48 per cent). Myocardial infarction preceding the mesenteric infarction by < 4 months was found in six patients (7 per cent).

Thirty-two patients (40 per cent) were hospitalized for an incorrect diagnosis before laparotomy ($n=30$) or autopsy ($n=2$). The most common misdiagnoses were acute pancreatitis in 10 cases, diverticulitis in 8, strangulation ileus in 7, appendicitis in 5 and perforated peptic ulcer in 2.

Aetiology

The aetiology of mesenteric infarction related to hospital mortality is presented in *Table 1*. Acute occlusion of the SMA was responsible for 60 per cent (49/81) of the cases and the most common cause was an embolus. The distinction between thrombosis and embolus could not be made at laparotomy or autopsy in only one case. The highest mortality was observed in the group of patients with thrombosis of the SMA. The elevated median age (77·4 years) and the fact that proximal obstruction of the SMA had resulted in extended bowel damage (12 of 15 patients with SMA thrombosis had ischaemic bowel extending over 1·5 m) explain the poor prognosis.

Five patients with mesenteric venous thrombosis had predisposing conditions, namely cirrhosis ($n=2$), sepsis ($n=2$) or a previous abdominal operation ($n=1$) and four of these patients died. Four patients had primary venous thrombosis (i.e., lack of any predisposing factor) and all survived. The median duration of pain before admission in patients with venous thrombosis (7 days) was significantly longer

Table 1 *Aetiology of mesenteric infarction related to patient age and mortality*

	Number*	Age (median)	Mortality†
Superior mesenteric artery occlusion			
Embolus	33 (41%)	69·2 years	28 (85%)
Thrombosis	15 (18·5%)	77·4 years	14 (93%)
Unclear	1		
Venous thrombosis (predisposing factors)	5 (6%)	77·6 years	4 (80%)
Venous thrombosis (primary)	4 (5%)	63 years	0
Non-occlusive	15 (18·5%)	66·5 years	10 (67%)
Arteritis	2 (2%)	33 years	1
Others	6 (7%)	76 years	4 (67%)
Postoperative	13 (16%)	70 years	12 (92%)

Values in parentheses are percentages
* Percentages refer to the total of 81 patients; † Percentages refer to the number of cases with each aetiology, respectively

than those with other aetiologies (2 days), ($P<0{\cdot}0001$; Wilcoxon–Mann–Whitney U test)[15,16].

No vascular obstruction or other causes of ischaemia could be determined in 15 patients, 10 of whom (67 per cent) died during their hospital stay. Patients in this group and those with primary venous thrombosis were younger (median age: 66·5 and 63 years respectively) than those with SMA or secondary venous occlusion (median age: 72·3 years; $P<0{\cdot}005$, Wilcoxon–Mann–Whitney U test).

Arteritis as a cause of infarction was found in two young patients (27 and 35 years), one with scleroderma and the other with an atypical collagen vasculitis.

Other uncommon aetiologies included thrombosis of the inferior mesenteric artery with infarction localized in the left colon ($n=2$), multiple venous and arterial thrombosis in a patient having oestrogen therapy for carcinoma of the prostate, peripheral arterial occlusion caused by cholesterol emboli in the sigmoid colon in a patient shortly after cardiac surgery, obstructive infiltration of the SMA by a small bowel carcinoid and disseminated intravascular coagulation after cardiac surgery with massive bowel infarction.

Postoperative mesenteric infarction ($n=13$) occurred after abdominal surgery in six cases, after cardiovascular surgery in four and after other procedures in three. All but one of these patients with postoperative infarction died.

Treatment

The standard management of mesenteric infarction remained the same during the whole review period. In 37 patients treatment was withheld either in the emergency room ($n=12$; all of these patients were moribund and aged more than 77 years or at laparotomy ($n=25$) on the grounds of the extent of the bowel infarction (>2 m). These 37 patients were treated only by supportive measures and all died between 1 h and 8 days (median: 2·5 days).

The remaining 44 patients were treated primarily with curative intention. Bowel resection was carried out in 33 patients and was associated with embolectomy in 4. Embolectomy alone as primary treatment was performed in five patients. In two patients apparently adequate perfusion of the intestine was restored during laparotomy by peripheral venous infusion of 500 ml of dextran 40 and bowel resection was judged unnecessary. A second look was performed in 19 patients, but a secondary curative procedure was possible in only 6 of them.

Some form of antithrombotic prophylaxis was used in all cases treated with curative intention. Dextran 40 or 70 alone was used in 34 cases and was associated with low dose heparin in 7 cases or with intravenous heparin in therapeutic doses in 3 cases. Long-term anticoagulation with coumarin (over 4 months) was used in 12 patients while 2 were put on platelet aggregation inhibitors.

Results

Clinical course

Sixty-one of the eighty-one patients (75 per cent) died in hospital after an interval of 4 h to 32 days (median: 6 days) after admission. Of the 20 patients who left the hospital (45 per cent of the operated patients), 9 died subsequently. The cause of death could be ascertained in eight cases and only one had sustained further mesenteric infarction, which occurred 4 years later. Eleven patients are still alive and clinical assessment was possible in ten at intervals of 2 to 16 years after their operation. Seven of these patients do not complain of abdominal symptoms and three suffer from moderate diarrhoea without signs of malabsorption. Patients still alive had a median age of 60·5 years at the time of infarction compared with 76 years for the patients who died after hospital discharge ($P<0{\cdot}001$, Wilcoxon–Mann–Whitney U test).

Prognostic factors

Some factors were associated with a high hospital mortality. When investigated independently from each other by the Fisher exact probability test, the following factors recorded in the emergency room were significant ($P<0{\cdot}05$) in predicting a fatal outcome: clinical signs of peritonitis ($n=38$), symptomatic cardiac failure ($n=39$), leucocytosis >15 000/mm^3 ($n=54$) and at the first laparotomy, infarction of more than 1·5 m of bowel ($n=40$).

Two other factors were not significant in helping to predict a fatal outcome, probably due to the small sample size, namely recent myocardial infarction ($n=6$; $P=0{\cdot}1$) and intestinal perforation at the first laparotomy ($n=4$; $P=0{\cdot}57$).

Since some of these factors are interrelated, the software ALLOC 80[17] was used to assess interdependent significance. The prognostic value of the combination of three of these factors in assessing the risk of fatal outcome is presented in *Table 2*.

Curative treatment and clinical course

Among the 44 patients treated with curative intention at first laparotomy, 20 (45 per cent) have survived. Fourteen (32 per cent) died of an early recurrence of mesenteric infarction, proved by a second look operation or by autopsy. Ten (23 per cent) died of causes other than mesenteric ischaemia and the absence of intestinal damage was demonstrated by autopsy in all cases; the cause of death was always related to a cardiac disease.

As shown in *Figure 1*, all five patients initially treated by embolectomy alone died of a recurrence of the mesenteric infarction. Patients treated by resection alone or resection plus revascularization showed no difference in their clinical course. At histology, all these patients had normal resection lines. One of the two patients with spontaneous recovery of perfusion at laparotomy subsequently died of an extended recurrence of intestinal ischaemia. No arterial or venous occlusion was found at autopsy in this patient.

Discussion

Among the 81 patients with mesenteric infarction only 44 could be treated initially with curative intent. Of these patients 32 per cent died from an early recurrence of mesenteric ischaemia whereas 23 per cent died from other causes. This high rate of recurrence is a better indicator of the efficiency of management than is mortality, which often depends on factors other than mesenteric ischaemia. For example, significant cardiac disease in old and critically ill patients is related to a high mortality rate. However, early recurrence of mesenteric ischaemia represents the primary cause of treatment failure.

All but one of the twenty patients who were discharged did not experience further mesenteric infarction. The liberal use of

Table 2 *Prognostic factors and outcome—combination of three interrelated factors allowing prediction of the probability of fatal outcome*

Clinical signs of peritonitis	Symptomatic cardiac failure	Leucocytosis above 15 000/mm^3	Probability of death (%)
–	–	–	15
+	–	–	75
–	+	–	60
–	–	+	45
+	+	–	99
+	–	+	85
–	+	+	95
+	+	+	99

+ Factor present in the emergency room
– Factor not present in the emergency room

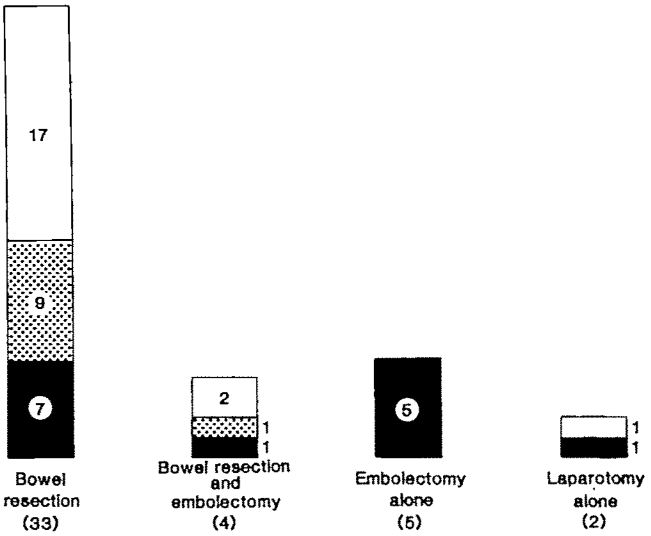

Figure 1 *Initial surgical procedure and clinical outcome in 44 patients treated with curative intent. Numbers represent the number of patients.* □, *Survivors;* ▨, *deceased without infarction recurrence;* ■, *deceased with infarction recurrence*

anticoagulation might explain the favourable long-term result in such patients and all had received intra-operative and postoperative dextran, while 14 were put on a long-term anticoagulation. Any attempt to improve results of treatment by revascularization and/or bowel resection must focus mainly on the prevention of early recurrence.

Experimental prevention of intestinal tissue damage due to ischaemia, vasoconstriction or reperfusion has been studied widely. Recently some authors have pointed out the role of substances injected either intravenously or directly into the SMA as a means of improving the survival rate in animal models. Although the mechanism of action of most of these substances is incompletely known, some are of interest in the treatment of mesenteric infarction in humans.

Oxygen-derived free radicals have been incriminated in the pathogenesis of reperfusion tissue damage. Attempts have been made to prevent such damage by using competitive inhibitors of purine metabolism such as allopurinol or specific scavengers such as superoxide dismutase (SOD)[18–22]. Clinical application of SOD is premature but allopurinol is commonly used to treat gout, and is well tolerated and inexpensive. As adjuvant therapy, allopurinol offers promise. Other studies in rats have demonstrated that intravenous injection of glucagon, methylprednisolone or prostacyclin (PGI2) improved the survival rate after SMA ligation[23]. Glucagon[24,25] and prostacyclin[25] were also effective when injected directly into the SMA. Glucagon has been considered to be of value in numerous models using rats, cats and dogs and is thought to increase flow significantly in the SMA and enhance oxygen diffusion into the intestinal tissue[23,25–28]. It seems in pharmacological doses safe for use in man[29]. Interestingly, with all these substances, prevention of intestinal tissue damage *in vitro* depended directly on the delay between the start of ischaemia and the administration of the substance studied. Thus, the clinical use of such substances would have to begin in the emergency room when mesenteric infarction was suspected.

Recent clinical studies have demonstrated an improved survival rate following early diagnosis and aggressive management using pre-operatively arteriography and selective SMA injection of vasodilators such as papaverine[10,13,14], phenoxybenzamine[7], prostaglandin E1[14] or adenosine triphosphate[12]. Vasodilators are of value in preventing persistent vasoconstriction in non-occlusive infarction[7,8,10–12,14], but may be of value in all forms of mesenteric infarction[9–11,13,14].

However, according to Marston[30], arteriography findings do not always correlate with bowel ischaemic damage. A patent arterial tree does not exclude infarction but, on the other hand, an occluded SMA does not prove its presence. In addition, routine pre-operative arteriography could lead to loss of time in a process where the time interval between admission and operation influences survival[1,9,30–33] and might delay effective treatment in patients who did not have mesenteric infarction.

Nevertheless, arteriography remains the best way of assessing mesenteric infarction pre-operatively. It defines the site and type of vessel occlusion, thus allowing expedient revascularization according to the nature of the obstructive process. As proposed by Bergan *et al.*[34] and Ottinger[35], proximal obstruction of the SMA is almost exclusively caused by a thrombosis and should be corrected by an aorto-mesenteric bypass. Successful thromboendarterectomy is exceptional[36,37], but reversal of proximal and subtotal occlusion of the SMA by percutaneous transluminal balloon angioplasty has been reported recently[38]. More peripheral obstruction (as far as the origin of the ileocolic artery) is almost always caused by emboli and catheter embolectomy is indicated. For peripheral arterial obstruction or non-occlusive infarction, a vascular procedure is useless. Venous thrombosis, responsible for 5–20 per cent of cases of infarction has in most series a good prognosis following resection without any attempt at revascularization[31–33,39–42]. According to our data and previous reports[39–42], only primary venous thrombosis or hypercoagulability disorders actually have a favourable prognosis.

Selective infusion of a vasodilator or intraluminal balloon angioplasty in some severely ill patients with reversible bowel ischaemia could obviate the need for laparotomy. Pharmacological prophylaxis of ischaemic tissue damage and revascularization may help to limit the extent of bowel resection and revascularization must, therefore, routinely precede resection. Intra-operative assessment of bowel viability by Doppler sonography or fluorescein injections and observation by the Wood light may prove to be a useful tool for a better definition of the resection lines[43–45].

Postoperative anticoagulation is recommended by all authors, but controversy exists not only with regard to its starting point but also regarding pre-operative and long-term antithrombotic prophylaxis. Significant intestinal bleeding by early postoperative anticoagulation leads Boley *et al.*[13] to delay any form of anticoagulation until 48 h after surgery whereas Bergan *et al.*[34] used heparin in prophylactic doses routinely and immediately after surgery. Dextran 40 or 70 (50 g per day for 5 days) perfused immediately after arteriography could represent an interesting alternative and in our experience dextran administration has never been followed by significant intestinal bleeding.

In conclusion, it can be argued that the classical treatment of mesenteric infarction including laparotomy with revascularization and/or bowel resection should now be accompanied by a pharmacological prevention of mesenteric vasoconstriction and reperfusion tissue damage if a high rate of recurrent ischaemia is to be avoided. Some effective substances—well documented in animal models and having no major side-effects in man—have yet to be applied to the problem of human mesenteric infarction. Arteriography offers the best assessment of infarction and allows expedient revascularization and access for selective perfusion with vasodilators.

Owing to the relative rarity of mesenteric infarction, multicentre collaboration and data collection are necessary to develop and improved approach. Before prognostic factors assessment (*Table 2*) leads to the withholding of curative treatment, further prospective studies with new therapeutic concepts are necessary. In our opinion, such studies should include assessment of the value of: (1) immediate intravenous therapy to minimize vasoconstriction and reperfusion tissue damage (for instance therapy with allopurinol or glucagon); (2) arteriography with selective perfusion of vasodilators into the SMA; (3) ±laparotomy with bowel resection and/or revascularization; and (4) routine prophylactic anticoagulation.

Acknowledgement

The authors wish to express their thanks to Mr M. W. Buser MS from the University Computer Centre of Basle for assistance with the statistical analysis of the data.

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Paper accepted 15 January 1987

Br. J. Surg. 1987, Vol 74, June,
504–507

Early results of low dose intra-arterial streptokinase therapy in acute and subacute lower limb arterial ischaemia

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Thirty-two patients with acute and subacute limb-threatening peripheral arterial ischaemia were treated with low dose intra-arterial streptokinase infusions. The mean duration of infusion was 38 h. Six patients developed pericatheter thrombosis and two had distal embolization of fragments of thrombus but in all cases these responded to repositioning the catheter and continuing the infusion. Five patients developed groin haematomata and in three of these there was evidence of a systemic fibrinolytic effect from the streptokinase with plasma fibrinogen reduced below 1 g/l. The most serious complication was perforation of the popliteal and tibial arteries which occurred on two occasions and required cessation of the infusion. Twenty-two patients (69 per cent) achieved limb salvage, eight (25 per cent) suffered a major amputation and two (6 per cent) died. The outcome was not related to the site, nature or duration of the arterial occlusion but patients with loss of sensation or paralysis of the affected limb were significantly less likely to obtain limb salvage ($P=0{\cdot}001$)*. For occlusions greater than 30 cm in length a new technique was used where the thrombus was lysed from distal to proximal in short lengths by gradual catheter withdrawal. This was successful in five out of six cases. Low dose intra-arterial streptokinase has been confirmed as an effective, relatively safe method of treatment in recent arterial ischaemia and can be recommended in situations where the results of surgery may not be favourable. In particular, patients with arterial thromboses and no distal run-off, distal and late arterial emboli, thrombosed popliteal aneurysms and patients after a failed embolectomy, have all been shown to respond to thrombolytic therapy with intra-arterial streptokinase.*

Keywords: Arterial thrombo-embolism, fibrinolysis, streptokinase

The management of patients with acute lower limb arterial ischaemia can be difficult. There is no doubt that patients with acute large vessel emboli benefit from urgent balloon catheter embolectomy[1,2], but surgery may not be so successful in patients with distal small vessel emboli[3] and emboli more than a few days old[2,4–5]. In addition, at least one-fifth of patients with acute and subacute arterial ischaemia have an arterial thrombosis[6] and thrombectomy alone in these patients may merely add intimal damage in a situation where thrombosis had already occurred. For this reason the role of thrombolytic therapy for acute arterial occlusions, especially in the high risk groups, is again under investigation[7].

Thrombolytic therapy using streptokinase has been used in peripheral arterial ischaemia since 1962[8]. Initially, large doses of streptokinase were given, usually intravenously, to induce a systemic lytic state to try to improve patients with acute ischaemia[9,10]. The treatment benefited about one-third of the patients but the systemic lytic state was responsible for a high incidence of haemorrhagic complications including fatal intracranial or retroperitoneal haemorrhage in about 3 per cent[11]. The technique did not become widely used until 1974 when Dotter described the method of low dose catheter directed streptokinase perfusion[12]. This involved infusing streptokinase at one-twentieth of the intravenous dose via a catheter inserted into the arterial occlusion and was designed to produce the maximum local thrombolytic effect with the minimum of systemic fibrinolysis. Several authors have published encouraging results using the technique with clot lysis rates averaging 71 per cent[12–20].

For the last year a modification of this technique has been used in Nottingham in a selected group of patients who would not have been expected to have a good outcome from conventional surgical management. The present report details early results in the first 32 patients. The results have been analysed to try to determine which patients benefited most from streptokinase therapy in order to provide guidelines for the management of this difficult and complex condition.

Patients and methods

The same management plan has been used for the past 12 months in patients with lower limb-threatening arterial ischaemia of less than 1 month's duration, as estimated from the clinical history. Many patients with arterial thromboses could identify the day on which their symptoms appeared despite not seeking medical advice for days or even weeks. Patients with symptoms for less than 5 days and a clinically obvious embolic source had an urgent surgical embolectomy. Remaining patients with severe arterial ischaemia (loss of sensation or muscle paralysis), who may suffer irreversible muscle necrosis after as little as 12 h, were therefore assessed with urgent arteriography. Those with suitable distal run-off vessels had prompt bypass surgery, as the length of time required for successful thrombolysis would have been too long to prevent irreversible muscle necrosis. The remaining 40 patients constituted a poor risk group and were therefore considered for thrombolytic therapy. All were assessed by arteriography. In eight it was not possible to insert an arterial catheter because of technical reasons.

Table 1 *Site and nature of the arterial ischaemia*

Site	
Iliac	3 (9%)
Femoral	17 (53%)
Popliteal	11 (34%)
Tibial	1 (4%)
Cause	
Arterial thrombosis	24 (75%)
Arterial embolus	4 (12·5%)
Post-procedure thrombosis (bypass graft, embolectomy, arteriogram)	4 (12·5%)

Patients

Thirty-two patients received thrombolytic therapy. There were 7 women and 25 men with a median age of 66 years (25–88 years). The median duration of ischaemia was 14 days (1–49 days). Five (16 per cent) patients were diabetics and 53 per cent were current cigarette smokers. Many of the patients were elderly with signs and symptoms of generalized atherosclerosis or a history of other thrombotic diseases. Two patients (6 per cent) suffered severe claudication and thirty (94 per cent) had ischaemic pain at rest, seven (22 per cent) of whom also had distal skin necrosis. Twelve patients (37 per cent) had severe ischaemia with loss of sensation or muscle paralysis.

In the study group of 32 patients, the mean ankle/brachial systolic pressure index was 0·29, but 12 patients (39 per cent) had no audible flow in the pedal arteries. The sites and causes of arterial ischaemia are listed in *Table 1*. Twenty patients (62·5 per cent) had no distal vessels suitable for conventional bypass surgery visualized at arteriography and would therefore have been suitable only for amputation. Contra-indications to treatment included recent active bleeding, stroke within the previous 2 months and any predisposition to haemorrhage, but did not include recent surgery. All patients gave informed consent to be treated.

Methods

A decision about treatment was made at the time of diagnostic femoral arteriography and, if required, a 4 Fr or 5 Fr polyethylene catheter was inserted 1 cm into the arterial occlusion. Antegrade Seldinger puncture of the ipsilateral femoral artery was performed for femoral and popliteal occlusions but contralateral femoral puncture was used for iliac occlusions.

The patients returned to the ward where they were nursed in bed with pulse and blood pressure recorded hourly throughout treatment. Streptokinase (Kabikinase, KabiVitrum) 5000 units/h was infused by syringe pump along with heparin 250 units/h to prevent pericatheter thrombosis. The effects of streptokinase on the fibrinolytic system were monitored throughout treatment with venous samples obtained before, after and 12-hourly during the infusion. Progress was monitored by arteriography performed after 4 h and every 12 h thereafter using portable X-ray equipment. Iopamidol (Niopam 300) was injected via the arterial catheter, 10 ml for femoropopliteal occlusions and 15 ml for iliac occlusions, and a single film taken at the end of the injection. The streptokinase infusion was continued until there was clinical improvement and angiographic reperfusion. There was usually improvement with each arteriogram, even up to several days, and if there was no change between two successive 12-hourly arteriograms continuation of the infusion was not worthwhile.

Low dose streptokinase will only lyse thrombus for 15–20 cm distal to the catheter tip. Therefore, in six patients with occlusions longer than 30 cm a new technique was used. The arterial cather was advanced through the thrombus to within 15 cm of its distal extent. Streptokinase was then infused until the vessel distal to the catheter was patent. The catheter was then withdrawn 10 cm into the thrombus and the infusion continued. In this way long occlusions were lysed from the distal end in 10 cm portions.

After completion of the infusion an angioplasty was performed on any residual stenosis, if possible before the catheter was removed. After successful recanalization the patients were anticoagulated with heparin for five days to prevent rethrombosis. As part of a further study the patients were then randomized to receive either long-term warfarin or antiplatelet therapy with aspirin 300 mg daily and dipyridamole 100 mg thrice daily.

After the infusion clinical examination and Doppler ankle pressures were performed and lysis recorded as successful or failed. In the week after treatment follow-up digital subtraction angiography and Doppler pressures were performed. The outcome at 30 days was recorded in terms of limb salvage, amputation or death.

Results

Of the 40 patients initially considered for thrombolysis the catheter could not be positioned in 8, usually because the occlusions were situated at the origin of the common iliac or superficial femoral arteries. Two of these patients received primary amputations and surgical reconstruction was attempted in the remaining six. Four patients had limb salvage after successful grafts, but in two the grafts failed resulting in one amputation and one death.

Therefore, 32 patients received streptokinase therapy and the infusion was completed without mishap in 29 (91 per cent). One patient who was critically ill before treatment died from continued thrombosis after 4 h (*Figure 1*). In two patients contrast extravasated from the popliteal and tibial arteries at arteriography and the infusion had to be stopped. One of these patients required urgent femoropopliteal bypass surgery for limb salvage and later died after 26 days from cardiac failure. The mean duration of infusion was 38 h (a total of 180 000 units of streptokinase) in the whole group and 39 h in those with initial successful lysis.

Initial complete lysis of the occlusion was observed on angiography in 22 of the 29 patients who completed the infusion. Eight patients had a residual stenosis treated by angioplasty. Despite successful reperfusion three patients required an amputation in the next 30 days, two for early rethrombosis (60 h and 72 h post-treatment) and one for extensive calf muscle necrosis. In seven patients vessel patency was not restored, five of whom had amputations and two had limb salvage at 30 days, one after a delayed embolectomy. In the successfully treated patients the mean ankle/brachial systolic pressure index was increased from 0·29 to 0·65. The overall results after 30 days were: limb salvage, 22 (69 per cent); amputation, 8 (25 per cent) and death, 2 (6 per cent).

The most frequent complication was pericathter thrombosis which occurred in six cases, usually when treating popliteal artery occlusions. This was always managed successfully by withdrawing the catheter and continuing the infusion. Distal embolization of fragments of lysing thrombus with worsening of limb ischaemia occurred twice and was also managed successfully by continued perfusion. Accidental catheter removal or fracture which occurred on four occasions was a nuisance and underlined the importance of secure fixation of the

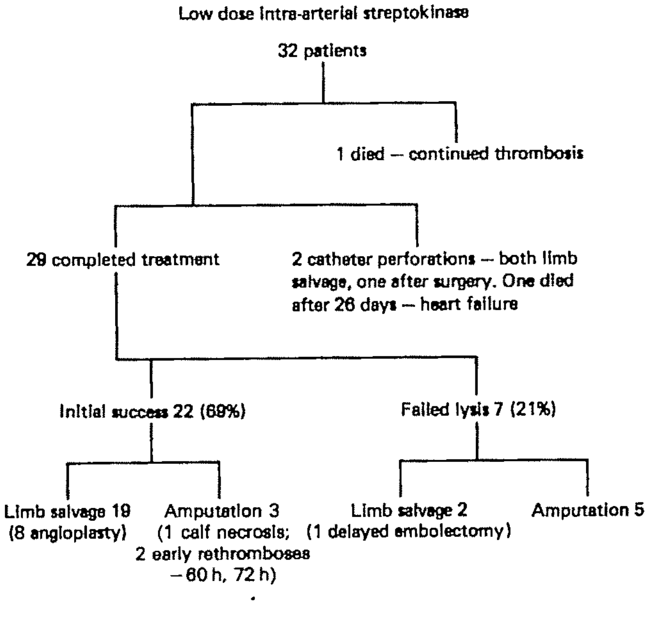
Low dose intra-arterial streptokinase
32 patients
1 died – continued thrombosis
29 completed treatment
2 catheter perforations – both limb salvage, one after surgery. One died after 26 days – heart failure
Initial success 22 (69%)
Failed lysis 7 (21%)
Limb salvage 19 (8 angioplasty)
Amputation 3 (1 calf necrosis; 2 early rethromboses – 60 h, 72 h)
Limb salvage 2 (1 delayed embolectomy)
Amputation 5

Figure 1 *Results of low dose intra-arterial streptokinase activity*

catheters. Five patients developed minor groin haematomata during treatment though none required blood transfusion. Systemic fibrinolysis with reduction of plasma fibrinogen below 1 g/l was seen in five (16 per cent) patients. Three of the five patients who developed a groin haematoma were in this group.

Successful lysis occurred in all cases of embolism, only one of four post-procedure thromboses and 15 (62·5 per cent) out of 24 arterial thromboses. The most important predictor of outcome was the severity of limb ischaemia at presentation. Only four of the twelve patients with loss of limb sensation or paralysis had limb salvage after 30 days compared with 18 of the 20 patients with ischaemic rest pain alone ($\chi^2 = 11{\cdot}1$, $P = 0{\cdot}001$). The presence of distal skin necrosis did not affect the outcome, nor did the site or the age of the occlusion.

The outcome after the gradual catheter withdrawal technique was not worse despite the greater length of the occlusions, five of the six cases having successful recanalization. However, the mean duration of the infusion in this group was longer at 50 h.

Discussion

Even in the most recent reports, patients with acute peripheral arterial ischaemia treated with conventional surgical techniques have only a 70 per cent chance of surviving to leave hospital with the limb intact[21–25]. Of the remainder, half die in hospital and half require a major amputation. Despite the surgical advances of the last 50 years the risk to life has remained the same as the risk to the limb[26,27]. There is no doubt that patients with acute large vessel emboli benefit from urgent embolectomy though, compared with thromboses, patients with emboli have a higher mortality due to associated cardiac conditions[22,24–25]. Thrombectomy alone for acute thromboses, especially below the inguinal ligament, is frequently not enough to achieve limb salvage and this may be the reason for the greater frequency of amputations after thromboses when compared with emboli[6,22,24–25,28]. Conventional arterial bypass techniques may be used in suitable patients with acute arterial thromboses and graft patency similar to that after routine surgery has been reported[28]. However, this is not a universal finding and many patients have no distal run-off vessels for bypass leaving amputation as the only resort. The recent development of new thrombolytic regimes has provided an alternative method of management which may be especially useful in high risk patients.

The high doses of streptokinase initially used both by intra-arterial and intravenous routes in peripheral arterial occlusions produced many haemorrhagic complications which were fatal in a small but significant proportion of patients[9–11]. Although the technique of low dose intra-arterial streptokinase perfusion was decribed in 1974[12] it was ignored until 1982 when a large series of patients was reported using the technique[13]. Since then other centres have reported in open trials that low dose streptokinase is a safe and effective method of treatment for peripheral arterial occlusions[14–20].

A systemic fibrinolytic effect may be produced during the infusion despite the low dose[16–18], but the risk of haemorrhagic complications is less than that recorded using intravenous streptokinase[15]. However, a mortality rate of about 1 per cent is still reported usually from stroke or concealed haemorrhage[15,17]. A plasma fibrinogen below 1 g/l is agreed as a risk factor for haemorrhage[17] and it may be possible to reduce complications further by lowering the dose of streptokinase if this level is reached[16]. However, some patients with bleeding complications have no evidence of systemic fibrinolysis[15,17]. Specific complications of the technique including pericatheter thrombosis and distal embolization are recognized but continued streptokinase infusion has usually resolved these problems[14,20,29]. Pericatheter thrombosis may be reduced by heparinization during treatment but this increases the risks of bleeding[14]. Concomitant use of low dose heparin does not entirely abolish pericatheter thrombosis but does not increase the risk of bleeding[15,16] and may also improve the thrombolytic effect of streptokinase[30]. Distal embolization of fragments of lysing thrombus with deterioration in the condition of the limb may necessitate surgical embolectomy if there has been no improvement after 4 h of continued streptokinase perfusion. Catheter perforation of popliteal and tibial arteries has not been previously reported but occurred twice in this series. In one case this was probably due to the catheter avulsing a geniculate vessel in which it was wedged after knee flexion[31]. In the second case contrast extravasated from the tibial artery 5 cm distal to the catheter tip which may represent an unwanted effect of streptokinase on an ischaemic artery.

In this and other series the overall early success rate of treatment is about 70 per cent. Long-term vessel patency has been reported as 70 per cent at one year if the recanalization lasted two weeks[13]. The use of angioplasty to treat any underlying arterial stenoses may prevent rethrombosis[13,16]. Long-term warfarin or antiplatelet therapy is often recommended[13] but objective evidence that either of these regimes is effective in prevention of rethrombosis is lacking.

The patients who have benefited most in open trials are those with arterial occlusions less than one month old, through lysis rates above 50 per cent have been reported three months after occlusion[13]. Patients with severe ischaemia, loss of sensation and paralysis of the affected limb, may have irreversible muscle necrosis after as little as 12 h and in these patients the time taken to achieve recanalization using thrombolysis may be too long. A surgical approach is probably superior in these patients. Revascularization of dead muscle can lead to a 'crush syndrome' with myoglobinuria and renal failure[19]. In common with the findings of others, in the present study patients with severe ischaemia were less likely to achieve limb salvage[20]. Short occlusions with patent distal vessels are more frequently lysed than long occlusions[13], and in most series emboli lyse more frequently than thromboses[15]. Vascular grafts may be more difficult to treat[32] and in Dacron grafts inserted within two months thrombolysis may cause extravasation through the graft[33]. Graft lysis may not be successful where the cause of occlusion is progression of distal disease[32]. The site of occlusion whether above or below the inguinal ligament has not yet been shown clearly to affect the lysis rate[20].

From the available data it is possible to suggest that low dose streptokinase may be specifically indicated in patients known to have a poor outcome from conventional surgery. These include arterial thromboses with no distal run-off, distal and late arterial emboli[34] and acutely thrombosed popliteal aneurysms where the risk of amputation is high[35]. The method may be used in the postoperative period and may be especially useful after an unsuccessful embolectomy[36–38]. Less specific indications include recent arterial thromboses which are operable but occurring in frail, elderly patients who constitute a poor surgical risk. Streptokinase perfusion is less invasive than surgery and has the advantage that if successful, the native vessel rather than a graft is left as the conduit for blood. However, until large, well designed trials comparing thrombolytic therapy with standard surgical treatment have been performed, the exact role of thrombolytic therapy will not be known. The main problem in interpreting trials in patients with acute ischaemia is the varied nature of the condition and the lack of data presented in reports on the patients. It is important for all studies of acute arterial occlusions that the severity of ischaemia and the site, length, duration and nature of the occlusion and its distal run-off are stated.

Several new agents with a theoretical specificity for fibrin have recently been produced and may be safer, more effective thrombolytic agents[39]. Tissue plasminogen activator, pro-urokinase and acylated plasminogen–streptokinase activator complex are all currently under investigation[40,41]. Until these new agents have been evaluated, low dose streptokinase treatment has been shown in this study to be effective and relatively safe in a group of patients with a poor outlook from conventional surgery. Although precise indications for its use are not yet clear, the technique is suitable for use in any hospital and no sophisticated equipment is required. Cooperation is necessary between surgeon, radiologist and haematologist for best results with the minimum risk of complications.

Acknowledgement

We would like to thank KabiVitrum for supporting this study.

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Paper accepted 19 January 1987

Br. J. Surg. 1987, Vol. 74, June,
508–510

Effect of defibrinogenation on the early patency rate of experimental small calibre arterial grafts

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The effect of defibrinogenation with Arvin was studied in a new animal model of early thrombosis of a 3 mm diameter polytetrafluoroethylene (PTFE) graft with a poor run-off. Fifteen control animals were compared with fourteen animals treated with subcutaneous Arvin 20 units* kg^{-1} *body weight* day^{-1}*, starting 2 days before surgery and continuing for 2 days postoperatively. The peroperative fibrinogen level in the controls was* $2{\cdot}8 \pm 0{\cdot}9\ g\ l^{-1}$ *compared with* $0{\cdot}4 \pm 0{\cdot}3\ g\ l^{-1}$ *in the treated group. There was no significant difference in the peroperative or postoperative platelet count or haematocrit value between the two groups. Plasma viscosity and whole blood viscosity (at a low shear rate of* $0{\cdot}7\ s^{-1}$*) were significantly less during and after surgery in the defibrinogenated group. The degree of defibrinogenation in these animals produced no problems with haemostasis during surgery or in the postoperative period. The cumulative patency rates of the controls at 24 h, 48 h, and 4 days were 43 per cent, 28 per cent and 28 per cent compared with 86 per cent* ($P < 0{\cdot}05$)*, 73 per cent* ($P < 0{\cdot}05$) *and 73 per cent* ($P < 0{\cdot}05$) *respectively in the defibrinogenated group. In this model of a narrow PTFE graft with a poor run-off, defibrinogenation was a safe and effective method of improving early patency of small calibre arterial grafts.*

Keywords: Blood vessel prosthesis, thrombosis, defibrinogenation

One of the main problems in vascular surgery is early thrombosis of small calibre arterial grafts. The occlusive rate in prosthetic below-knee femoropopliteal bypasses and infrapopliteal bypasses varies between 15 and 28 per cent at one month[1,2]. The results are even worse in conditions of high distal resistance where there is a poor graft blood flow[3].

Arvin (ancrod) is a thrombin-like enzyme derived from the venom of the Malayan pit viper. It causes rapid, effective and safe defibrinogenation by breaking down plasma fibrinogen to form fibrin polymers which are less stable than thrombin-formed fibrin[4]. These microclots, being unstable, are readily removed from the circulation by the reticulo-endothelial and the fibrinolytic systems[5] resulting in a rapid appearance of circulating fibrinogen degradation products (FDP)[6]. Arvin has no direct effect on the coagulation system other than fibrinogen[4], nor on the platelets[7]. Defibrinogenation has been used in several clinical conditions: intermittent claudication and more severe degrees of chronic leg ischaemia[8], and in the prevention of deep vein thrombosis and thrombo-embolic conditions[9]. It has also been used to protect venous grafts[10–12] and in extracorporeal circulation systems[13]. This paper presents a study of the effect of Arvin on acute graft thrombosis using a new animal model which has been previously described in detail[14].

Materials and methods

New Zealand white male rabbits with an average weight of 3·2 kg were used. Under general anaesthesia and using microsurgical techniques a 2 cm long and a 3 mm internal diameter polytetrafluoroethylene (PTFE) graft was inserted into the infrarenal aorta. The distal run-off was decreased by applying clips of standardized gaps to both common iliac arteries. The clips narrow but do not occlude the vessels, reducing the aortic flow by approximately 50 per cent. Five minutes before cross-clamping of the aorta, all animals received heparin in a single intravenous dose of 100 units kg^{-1} body weight. Patency of the grafts was monitored three times daily by a Doppler ultrasound flow detector with the probe applied over the course of the femoral arteries. When Doppler signals could not be detected in either groin, thrombosis was confirmed by re-exploration.

Plasma fibrinogen levels were estimated by the Clauss method[15]. The Contraves low shear viscometer was used to measure whole blood viscosity at shear rates of 0·7, 2·3 and 94·5 s^{-1}. A Harkness capillary tube viscometer was used to measure plasma viscosity.

For scanning electron microscopy (SEM) the grafts were perfused through a cannula inserted into the aorta proximally at a pressure of 100 cmH_2O using 0·9 per cent sodium chloride first, followed by 3 per cent buffered glutaraldehyde for fixation *in situ*.

Arvin was administered in a dose of 20 units kg^{-1} body weight subcutaneously in a single daily dose, starting 48 h before operation and continued for 48 h postoperatively (*Figure 1*).

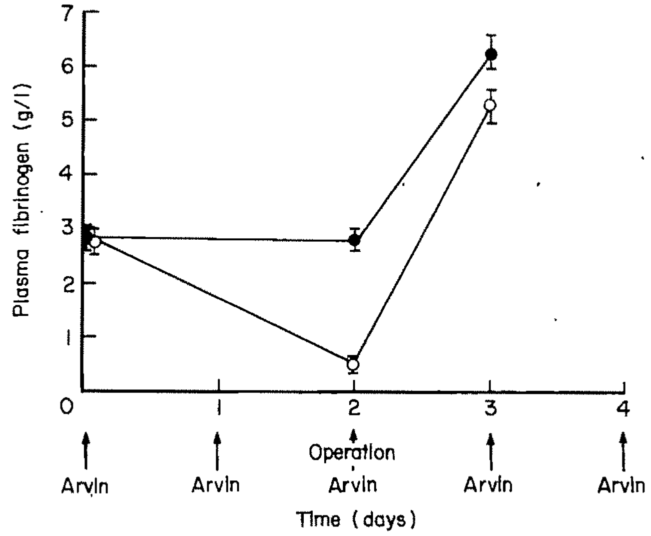

Figure 1 *The protocol of Arvin administration and the changes in the plasma fibrinogen level. Arvin dose 20 units (kg body weight)*$^{-1}$ *day*$^{-1}$ *subcutaneously;* ●*, controls;* ○*, Arvin*

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Table 1 *Whole blood and plasma viscosity (mean ± s.d.)*

	Arvin	Controls	Two-tailed *t* test
Peroperatively:			
Plasma viscosity (mPa s)	1·068 ± 0·055	1·15 ± 0·058	$P = 0·002$
Whole blood viscosity (mPa s)			
At shear rate			
0·7 s^{-1}	10·36 ± 2·5	13·74 ± 3·12	$P = 0·005$
2·4 s^{-1}	8·91 ± 1·47	10·41 ± 1·95	n.s.
94·5 s^{-1}	4·20 ± 0·33	4·12 ± 0·48	n.s.
24 hours postoperatively:			
Plasma viscosity (mPa s)	1·12 ± 0·108	1·33 ± 0·057	$P = 0·03$
Whole blood viscosity (mPa s)			
At shear rate			
0·7 s^{-1}	19·38 ± 6·04	31·51 ± 10·83	$P = 0·01$
2·4 s^{-1}	12·93 ± 2·75	16·80 ± 5·3	n.s.
94·5 s^{-1}	4·69 ± 0·505	5·05 ± 0·73	n.s.

n.s. = not significant

Results

A total of 32 experiments were carried out. Seventeen animals received Arvin and the remaining fifteen acted as controls. Three of the defibrinogenated animals were killed before the end of the observation period and the grafts, which were still patent, were harvested for SEM studies. All the other animals were observed for a minimum period of 4 days, unless the graft had occluded. There were no problems with haemostasis during the operation or postoperatively. There was no statistically significant difference between the controls and the Arvin group with regard to the peroperative or postoperative platelet count or haematocrit value. There was a small but statistically significant increase in white cell count in the defibrinogenated group (before Arvin $10·9 \pm 2·3 \times 10^9 l^{-1}$ and after Arvin $12·74 \pm 1·9 \times 10^9 l^{-1}$). The changes in plasma fibrinogen level in the Arvin group was $0·47 \pm 0·27 g l^{-1}$ compared with $2·8 \pm 0·88 g l^{-1}$ in the controls. Twenty-four hours postoperatively, the fibrinogen level in both groups was higher than that at entry (day 0) and there was a trend towards a difference between the two groups which did not reach statistical significance ($P = 0·07$). Whole blood viscosity and plasma viscosity were measured peroperatively and 24 h postoperatively (*Table 1*). SEM studies of the grafts in both groups did not show much difference although the amount of platelet deposition in the Arvin group was much less. Both showed fibrin mesh and some red cells. However, there was more white cell deposition on the grafts in the Arvin group.

All the animals were observed for a minimum of 4 days and five animals with patent grafts were observed for a period of 1–4 weeks. All the occlusions found in both groups occurred in the first 48 h. There was a significant difference in the graft patency rate between the two groups. The cumulative patency rates of the controls at 24 h, 48 h and 4 days were 43 per cent, 28 per cent and 28 per cent respectively while in the Arvin group they were 86 per cent ($P < 0·05$), 73 per cent ($P < 0·05$) and 73 per cent ($P < 0·05$) respectively (*Figure 2*).

Discussion

This study has shown that defibrinogenation with Arvin is effective in improving early patency in critical arterial grafts in this rabbit model. Similar results have been previously obtained in animal models of implanted grafts on the venous side[10–12]. There are several possible mechanisms for the beneficial effect of Arvin. Defibrinogenation has been found to increase blood flow especially at low shear rates, e.g. in critical arterial stenosis[16]. This will minimize the effect of the high distal resistance on blood flow. Plasma fibrinogen is the substrate for coagulation. Also, fibrinogen deposition on the graft greatly accelerates the rate of platelet deposition[17]. It is interesting that in humans, even within the physiological range of plasma fibrinogen level, platelet aggregability decreases in direct proportion to the plasma fibrinogen level[18]. Also the released FDP may cause inhibition of both platelets[19] and the coagulation system[5,6]. It is possible that with low fibrinogen less fibrin is formed and this may cause the thrombus to be less stable with a tendency to embolize distally[20]. Whether these micro-emboli have a deleterious effect on the circulation is uncertain.

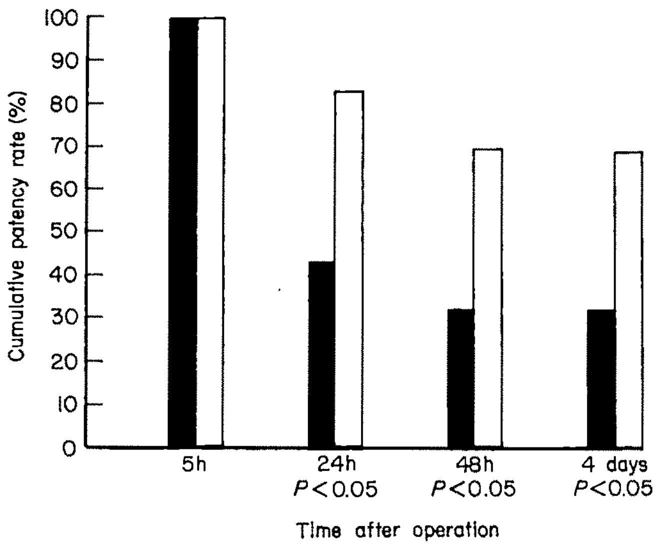

Figure 2 *Cumulative patency rate. Controls versus Arvin group. A histogram comparing the patency rate in the controls* ■ *($n = 15$) and Arvin-treated* □ *($n = 14$) group*

In this study, the improvement of patency in spite of the high fibrinogen level at 24 h postoperatively could be due to two mechanisms. It may be that the most critical period for graft–blood interaction is the first few hours, when the fibrinogen level was low. It is also possible that it is not the fibrinogen level that was important but the released FDP.

The effect of Arvin on the white cell count is interesting and has not been previously reported. However, as in the present study, Hanson *et al.* also noted that more white cells were deposited on the graft in Arvin-treated baboons than in the controls[20].

In this study there is no evidence that Arvin simply delays the onset of thrombosis as Arvin was discontinued after the second postoperative day and all the grafts that were patent at that time remained so for the whole period of observation (up to 4 weeks). An early critical period of high thrombogenicity followed by a longer relatively non-thrombogenic period is also typical of the grafts implanted in humans[1–3]. Measures to prevent thrombosis in the early critical period might protect the grafts and keep them patent for a longer time. There were no problems with haemostasis in these experiments. On the basis of this study, a multicentre clinical trial is being started using perioperative Arvin in conjunction with critical grafts.

Acknowledgement

The authors would like to thank W. L. Gore and Associates Ltd for covering part of the cost of this study, for supplying the GORE-TEX grafts and for the SEM studies at their laboratories in Flagstaff-Arizona.

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Paper accepted 9 January 1987

Surgical workshop

Br. J. Surg. 1987, Vol. 74, June, 510

Subcutaneous dartos pouch fixation for testicular torsion

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Testicular torsion is one of the commonest abdominal emergencies in children and young men. Various methods have been described to fix the testis after operative detorsion. We describe the technique of subcutaneous dartos pouch fixation for such cases.

Method

A transverse incision is made in the scrotal skin. Blunt dissection is performed deep to the skin to create a subcutaneous pouch (the degree of dissection depending on the size of the testis); dartos muscle is then incised transversely. The tunica vaginalis is opened widely in the longitudinal axis and the testicular detorsion is performed. Tunica is then reflected backwards behind the epidydimis and the cord. The testis is placed in the subcutaneous dartos pouch and some interrupted sutures of chromic catgut are placed in the dartos so that it fits snugly around the cord. The scrotal skin is sutured with chromic catgut (*Figure 1*). Contralateral orchidopexy is performed in a similar fashion.

Discussion

Subfertility is a recognized problem even after early and successful detorsion and bilateral fixation. It may be that testes prone to torsion also have defective spermatogenesis. Maldescended testes are ten times more prone to undergo torsion and the subcutaneous dartos pouch technique is the most secure way of fixing the testis in such cases. Testis placed in a subcutaneous pouch develops adhesions more easily and becomes firmly fixed. Moreover, the testis lies just deep to the skin without overlying tunica vaginalis and the dartos. This may, at least theoretically, result in improved spermatogenesis (although there is no practical evidence) and allow easier assessment of the size of the testis during the follow-up period. If investigation of subfertility is indicated, a testicular biopsy may be performed more easily when testis lies just deep to skin.

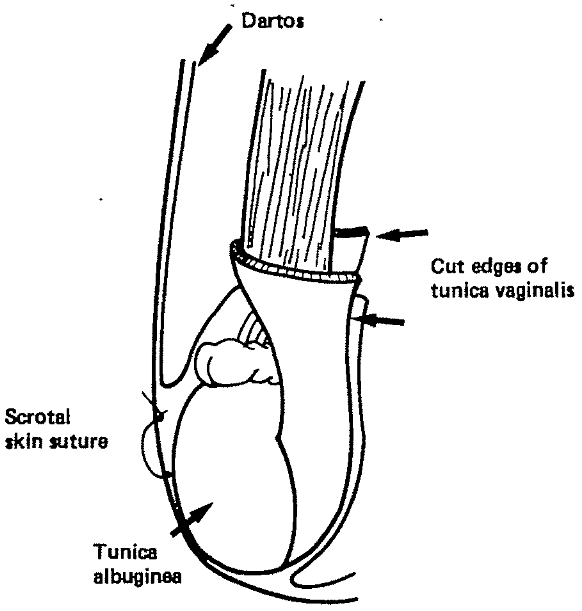

Figure 1 *Testis lodged in the dartos pouch*

Paper accepted 6 February 1987

Surgical Research Society

Br. J. Surg. 1987, Vol. 74, June,
511–515

The 65th Meeting of the Surgical Research Society took place on 8 and 9 January 1987 at The University of Surrey, Guildford. The Meeting was organized by The Academic Surgical Unit, St. Mary's Hospital Medical School, and Professor P. R. F. Bell was in the Chair. A Symposium entitled 'Surgical infection' preceded the Free Paper Sessions. Ninety-eight papers were read, and the Patey Prize was awarded to Mr D. R. Allen for his presentation entitled 'The effect of smoking on the permeability of the arterial wall'. A selection of papers and abstracts is published on pp. 511–48.

Anorectal temperature sensation: a comparison of normal and incontinent patients

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In the skin, temperature sensation plays an important role in discriminating between gas, liquid and solid. To elucidate the role of temperature sensation in idiopathic faecal incontinence we studied the minimum detectable temperature change in the lower, middle and upper zones of the anal canal and rectum in 33 normal subjects, and 20 patients with idiopathic faecal incontinence. A water perfused thermode was used to vary anorectal temperature from 37°C down to 32·5°C and up to 41·5°C. The temperature change was reported by the patient as the thermode temperature varied from 37°C to each extreme and on return to base line. The anal canal in the control group was highly sensitive to temperature change, the lower rectum was significantly less sensitive (P<0·0001). At each level in the anal canal and lower rectum the incontinent group were significantly less sensitive than their controls (P<0·005). The mid-rectum had no appreciable sensation in either group. We consider that this sensory deficit may be an important factor in idiopathic faecal incontinence.

Keywords: Anorectal temperature sensation, incontinence

There is considerable evidence that the motor nerves to the pelvic floor are affected by a neuropathic process in idiopathic faecal incontinence[1–21]. Roe *et al.*[22] reported sensory impairment in the anal canal of incontinent patients using mucosal electrosensitivity to test anal sensory thresholds. Whereas this technique probably quantifies tactile sensory awareness, temperature sensation in the skin elsewhere in the body plays an important role in the distinction between gas, liquid and solid and is involved in the appreciation of 'wetness'[23]. The anorectum also makes these distinctions allowing flatus to be passed whilst retaining faecal material in the normal subject. To elucidate the role of temperature receptors in the anal canal, we developed a new technique to study anorectal temperature sensation. In this paper we present the results of a comparison between normal control subjects and patients with idiopathic faecal incontinence.

Patients and methods

Studies were carried out in 20 women, median age 59·5 years (range 34–80) with idiopathic faecal incontinence. All the subjects had undergone the necessary clinical investigations and had long-standing symptoms of incontinence. For comparison we also studied 33 normal control subjects, 17 women and 16 men, median age 46·5 years (range 18–83) admitted to hospital with conditions unrelated to the colon, rectum and anal canal. They all had normal bowel function.

Ethical conditions

Informed consent was obtained from each individual. The study was approved by the Bristol and Weston Health Authority.

Design of study

A detailed history using a standard questionnaire was obtained from each patient with special reference to anorectal symptoms and relevant obstetric history. A full clinical examination was performed on each patient including digital examination of the anorectum and proctoscopy. In the incontinent patients sigmoidoscopy was also performed. No bowel preparation was used. Functional sphincter length was then measured by a standard station pull-through technique using a precalibrated water-filled microballoon catheter connected to an external transducer (Statham P23Gb, Spectromed, Coventry, UK) and the pressure recorded on a multichannel pen recorder (Hewlett-Packard 7758A, Massachusetts, USA).

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Thermal sensitivity

A specially constructed thermode was used to vary anorectal temperature. It consisted of a hollow brass bullet-shaped probe, 1 cm in length and diameter, through which water of different temperatures was circulated (*Figure 1 a and b*). It was connected to three thermostatically controlled water baths and two taps allowed the water being pumped through the thermode to be changed from one bath to another. The temperature of the baths was set such that with the probe in the anorectum its temperature could be maintained at 37°C and then either rapidly reduced to 32·5°C or increased to 41·5°C. These temperatures were chosen to provide a definite cold or hot stimulus without causing discomfort to the patient. The temperature at the mucosa–thermode interface was measured by a small thermocouple embedded in a groove on its surface. The temperature was continuously recorded on a Dantec chart recorder (Dantec system 2100, Copenhagen, Denmark). The anal canal was subdivided into three zones—lower, middle and upper—by dividing the manometrically measured high pressure zone into three parts. The thermode was inserted initially into the lower zone with its temperature at 37°C. After a short delay to allow the patient to become accustomed to the presence of the thermode, he or she was asked to indicate immediately if from that moment onwards a change in temperature was felt. The temperature of the thermode was then reduced to 32·5°C and an event marker on the chart recorder used by the investigator to denote the point at which the patient noticed a change. The procedure was repeated for the temperature shift from 32·5°C to 37°C and again for the two shifts from 37°C to 41·5°C and 41·5°C to 37°C. Four temperature shifts were therefore imposed on the anorectum (*Figure 2*). For each a measurement of the minimum detectable temperature change (MDTC) was recorded. The procedure was carried out in the lower, middle and upper anal canal. In addition the 1 cm zone of lower rectum just craniad to the anal canal and the mid-rectum, 10 cm from the anal verge were also studied.

Statistical analysis

The data were first analysed by a Kruskal–Wallis one-way analysis of variance. Individual sets of results were compared by the Mann–Whitney *U* test. To determine whether patient sex had any effect on temperature sensation a Kruskal–Wallis test was carried out on the control group, at each level in the anorectum, with each stimulus for men and women. Similarly the effect of age was studied using the same test on four age bands in the control group. (The age groups were designed to put approximately equal numbers in each group and were (i) under 32 years, (ii) 33–43, (iii) 44–57 and (iv) 58 and over.

Results

Clinical details

The control group had no anorectal symptoms. The patient group was incontinent to solid stool in 75 per cent of cases, the remainder being incontinent to a loose stool only. In addition to their presenting complaint of incontinence, 55 per cent complained of urgency, 45 per cent of incomplete rectal emptying, 20 per cent of prolonged straining at stool and 15 per cent of pruritus ani. The obstetric details of the female controls and incontinent group are given in *Table 1*.

Thermal sensitivity

Controls. In the lower zone of the anal canal of controls the average of the median MDTC was 0·8°C. The lowest median value was 0·6°C for the normal to hot temperature change (37–41·5°C) (*Figure 3*). Forty-two per cent of all temperature trials

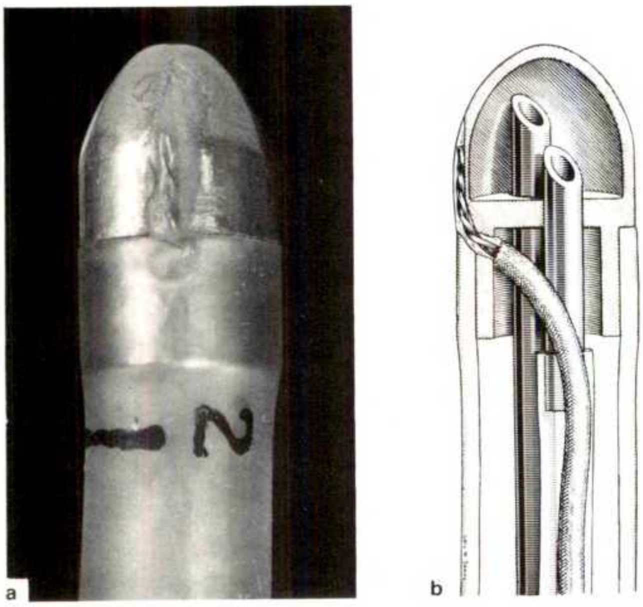

Figure 1 *The thermode, illustrating the thermocouple on its surface* (**a**) *and* (**b**) *its internal design*

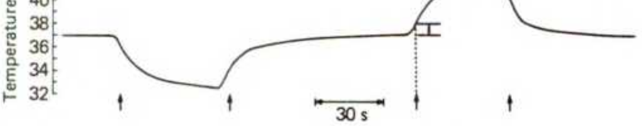

Figure 2 *Example of thermode temperature change from a control patient. Arrows indicate the point at which a temperature change was perceived*

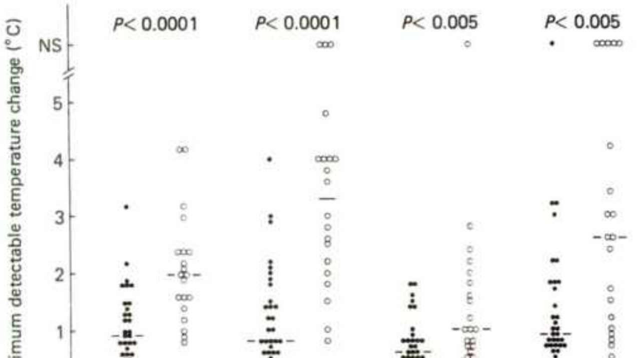

Figure 3 *Temperature sensation in the lower anal canal median MDTC values less than 1°C in controls with significant sensory impairment in incontinent patients.* ●, *Controls;* ○, *idiopathic faecal incontinence; NS, no sensation*

Table 1 *Obstetric data of female controls and incontinent group*

	Multiparous	Average parity	Long labour	Perineal tears	Forceps	Hysterectomy
Female controls ($n=17$)	94%	2·3	20%	52%	6%	23%
Incontinent group ($n=20$)	90%	2·5	6%	45%	30%	33%

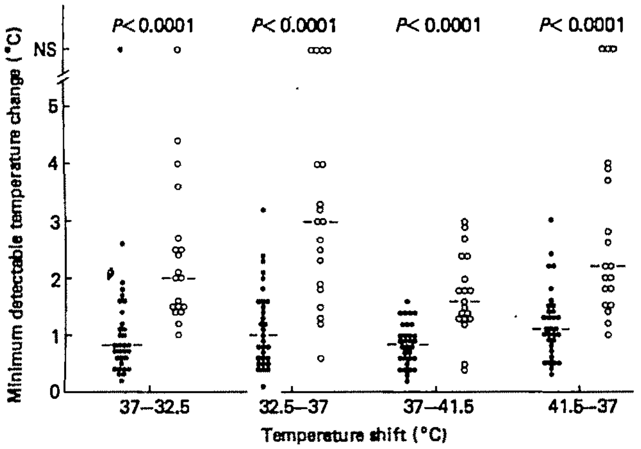

Figure 4 *Temperature sensation in mid-zone of anal canal. Results from both groups similar to lower zone.* ●, *Controls;* ○, *idiopathic faecal incontinence; NS, no sensation*

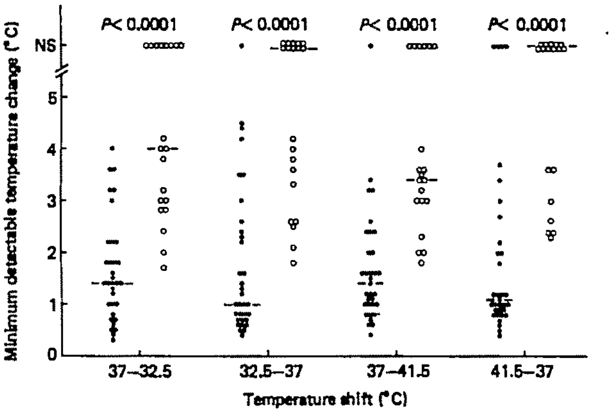

Figure 5 *Temperature sensation in upper anal canal. The incontinent patients had very poor sensation at this level.* ●, *Controls;* ○, *idiopathic faecal incontinence; NS, no sensation*

in this zone were felt at temperature changes of 0·5°C or less. In the middle of the anal canal the results were very similar; the average median MDTC was 0·9°C, the lowest median was 0·8°C for the normal to cold temperature change (37–32·5°C) (*Figure 4*). There was no statistical difference between the middle and lower zones for the four temperature changes. In the upper zone, in contrast to the lower and mid-zones of the anal canal, the most sensitive stimulus was a temperature change from each extreme to normal (32·5–37°C, median MDTC 1·0°C; 41·5–37°C, median MDTC 1·1°C (*Figure 5*). For these two temperature changes the entire anal canal was equally sensitive, there being no statistical differences between any zone. There was however a significant reduction in thermal sensitivity in the upper anal zone for the normal to cold and normal to hot temperature changes ($P < 0{\cdot}005$ and $P < 0{\cdot}0001$ respectively).

In the lower rectum very few sensory nerve endings have been reported[24], but the control group retained a definite though much reduced sensitivity to thermal stimuli, the median MDTC ranging from 3·4°C to 4·0°C (*Figure 6*). The difference between this zone and the upper anal canal was highly significant ($P < 0{\cdot}0001$ for all four temperature changes). In the mid-rectum, sensation was negligible. Seventy-five per cent of temperature trials were not felt at all, and one-third of the remaining trials were interpreted incorrectly (*Figure 7*). These results show that the normal anal canal is highly sensitive to thermal stimuli, particularly in the lower and mid-zones but the lower rectum is relatively insensitive. This trend of reduced sensitivity was continued in the mid-rectum with very few correct responses in this zone.

Incontinent patients. Compared with the control group the incontinent patients were significantly less sensitive to thermal stimuli at each level in the anal canal and lower rectum (*Figures 3–6*). No temperature trials were felt at all in the mid-rectum in the incontinent group (*Figure 7*). There was no statistical difference between control and incontinent patients in this zone. The most profound differences were in the middle and upper zones of the anal canal ($P < 0{\cdot}0001$ for each temperature change in both zones) (*Figures 3–7*).

Age/sex effects

Analysis of the data indicated that neither age or sex had any effect on thermal sensitivity.

Discussion

Denervation and reinnervation of the external anal sphincter is well recognized in anorectal incontinence[1-21]. Increased fibre density on single fibre electromyography has been attributed to stretch injury and obstetric trauma[4,5]. Conventional electromyography using prolongation of motor unit potential duration has been used to quantitate reinnervation of the external anal sphincter[10,12] and puborectalis[13] in idiopathic faecal incontinence. Muscle biopsies of the external sphincter and puborectalis show fibre grouping and compensatory hypertrophy in keeping with chronic partial denervation[1,2].

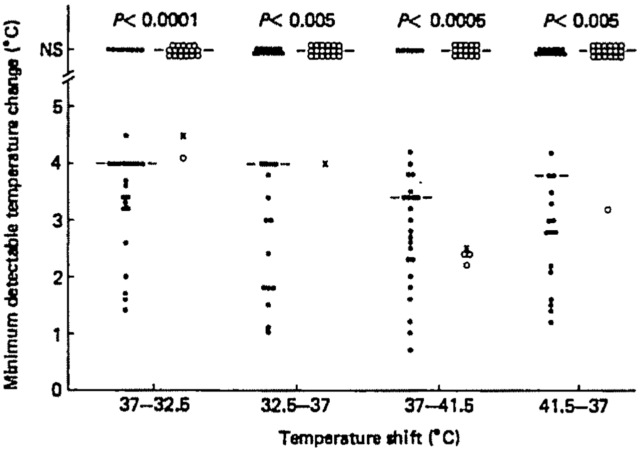

Figure 6 *Temperature sensation in lower rectum. This zone was much less sensitive than the anal canal; controls remain more sensitive than incontinent.* ●, *Controls;* ○, *idiopathic faecal incontinence;* ×, *incorrect sensation; NS, no sensation*

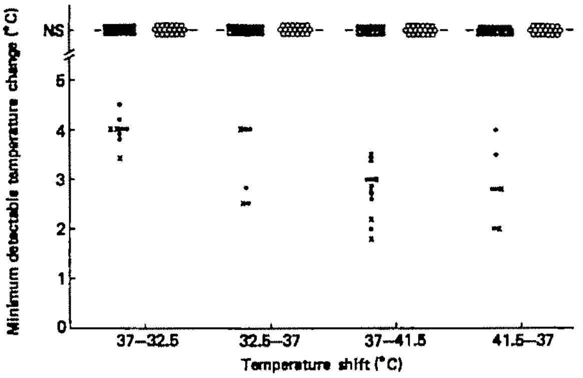

Figure 7 *Temperature sensation in mid-rectum. Both groups had negligible sensation at this level.* ●, *Controls;* ○, *idiopathic faecal incontinence;* ×, *incorrect sensation; NS, no sensation*

Nerve conduction studies employing pudendal nerve and spinal cord stimulation have reported slowed conduction velocity consistent with motor nerve damage[19,20]. The pudendal nerve is a mixed nerve. The pelvic nerves $S_{3,4}$ arising above the pelvic floor are also reported to be mixed nerves[25] although it is unclear what these direct branches contribute to normal anorectal sensation. It is to be expected that if the motor arc is impaired then a sensory deficit should be present in neurogenic anorectal incontinence. Indeed studies from this laboratory have demonstrated impaired mucosal electrosensitivity in patients with faecal incontinence[22].

Duthie and Gairns stained sections of the anal canal and lower rectum and studied the distribution and type of nerve endings[25]. In the material from ten human subjects they demonstrated a profusion of free nerve endings extending from the anal margin to the craniad anal canal as far as the top of the columns above the dentate line. In the rectal mucosa these nerve endings were observed to cease abruptly and in the ten patients studied only one organized ending was found. These authors proceeded to measure sensation quantitatively using horse hair to mimic light touch, pinprick to induce pain and a metal rod at either 4°C or 35°C to test temperature sensibility. Touch and pain stimuli were perceived in the anal canal up to 0·5–1·5 cm above the dentate line. Moreover, although poorly localized, painful stimuli were more vividly felt in the region of the dentate line than on the perianal skin. Likewise cold and heat were appreciated in the anal canal but for technical reasons the proximal extent of this sensation could not be determined. In their experiments none of the patients experienced rectal sensory awareness. Whereas the appreciation of these stimuli was largely subjective, an attempt was made by Roe *et al.*[22] to quantitate anal sensation objectively using square wave stimuli from a constant current generator delivered via a special probe to the anal canal. In this report the patient indicated the moment a constant sensation was felt in the anal canal. While a higher voltage stimulus would lead to pain, it is possible that the low voltage stimulus which was not noxious mimicked light touch.

Although light touch may be an important sensation, there is recent evidence that the discrimination between gas, liquid and solid by skin nerve endings may be dependent on normal temperature receptors[23]. This results from an appreciation of the thermal mass of the material palpated. Thus for example one can discriminate between plastic which feels relatively warm and metal which feels cold, yet both are at the same temperature. It is probable that the skin of the anal canal can sense the thermal mass of any medium it comes into contact with in the same way. The anorectum in normal subjects is able to discriminate between gas, liquid and solid. When one of these distends the rectum, the internal anal sphincter relaxes whilst the external anal sphincter contracts. Since the former contributes 80 per cent of resting and canal pressure, the net result is a fall in pressure with consequent opening of the anal canal. Duthie termed this sequence the sampling reflex[26] in which differential relaxation of the upper anal canal allows contact of rectal contents with the specialized sensory epithelium in the mid zone of the anal canal in the region of the dentate line.

In this study we developed a new technique to assess temperature awareness in the anorectum. We have shown that the anal canal is able to appreciate very small changes in temperature, and this is comparable to the most sensitive areas of skin in the rest of the body, namely the fingertips, the lips and the forehead[27]. No effect of age has been demonstrated in studies of thermal sensitivity in these latter two areas although a slight deterioration with increasing age has been found in the fingertip. The anal canal resembles the lip and forehead in that we could not demonstrate an increase in sensory thresholds with age. The lower and middle parts of the anal canal were significantly more sensitive to changes in anal temperature, less than 1°C, compared with the upper zones. Such a degree of sensory perception supports the concept of the sampling reflex described by Duthie and Bennett[26]. In studies of the recto-anal inhibitory reflex, following distention of the rectum by a balloon inflated with 20 ml of air, pressures in the upper and middle zones of the anal canal dropped[28]. It reinforces the role of contact of rectal contents with this specialized epithelium in the middle zone of the anal canal and its role in the sampling reflex.

The thresholds of thermal sensitivity were markedly impaired in patients with faecal incontinence. This impairment is compatible with damage to the sensory or afferent arc of the nerves to the anal canal. We suggest that reduced temperature awareness has a role in the pathogenesis of anorectal incontinence which may be mediated via a defective sampling response. Further studies are required to determine the relative importance of tactile and temperature sensation in the sensory arm of the continence mechanism.

Acknowledgements

This work was supported by a grant from the Medical Research Council.

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Br. J. Surg. 1987, Vol. 74, June, 516–519

A reliable and readily available method of measuring limb blood flow in intermittent claudication

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To evaluate isotope limb blood flow measurement in intermittent claudication we have assessed 58 non-diabetic patients comparing our new method with treadmill testing and Doppler assessment. Limb blood flow was applicable to all 58 patients; 25 patients were unable to walk on a treadmill and of the 33 who could 12 failed to walk for one minute, making a standard one minute exercise test inappropriate. In those patients who could perform exercise tests there was a significant correlation between maximum walking distance and limb blood flow ($r=0{\cdot}35$, $P=0{\cdot}02$). *Resting, post-exercise and post-hyperaemic ankle–brachial systolic pressure indices bore no relationship to the maximum walking distance. Isotope limb blood flow measurement is reproducible* ($r=0{\cdot}97$), *can be applied to those patients who cannot walk on a treadmill and provides information about both legs. It correlated significantly with all the other tests and can be recommended for the minimally invasive assessment of intermittent claudication.*

Keywords: Intermittent claudication, systolic pressure measurement, Doppler, blood flow measurement

Despite the efforts of many vascular laboratories, the assessment of intermittent claudication remains controversial.

The ankle–brachial systolic pressure index determined using a transcutaneous blood velocity detector (Doppler) is the simplest and most widely used objective measurement[1]. It is a useful initial screening procedure for a patient with suspected occlusive arterial disease[2] but is poorly reproducible in that a change of as much as 0·15 may not be significant[3]. Pressure measurements can be misleading and should only be a guide to diagnosis. Sclerosis of the arterial wall makes the vessel less easy to compress which leads to an overestimation of pressure. This is particularly true when there is medial calcification, a common finding in diabetics[4]. The technique can be extended to record multi-level segmental pressure which can localize haemodynamically significant lesions[4,5]. A further problem with resting tests is that they do not relate to the functional changes in flow following exercise.

Consequently, to evaluate a patient with intermittent claudication, many laboratories stress the circulation either by carrying out an exercise test or producing hyperaemic flow with arterial occlusion[6,7]. There is no doubt that treadmill testing is the most cogent physiological measurement, as it directly investigates the presenting symptoms, but there are practical difficulties. There is no accepted protocol for carrying out exercise tests and so comparison of results between centres is difficult. The pain-free walking distance and the maximum walking distance are subjective measurements and so are poorly reproducible[7]. In addition information is provided only for the most severely diseased limb. In an attempt to eliminate these problems measurement of the ankle systolic pressure after a standard one minute exercise test has been proposed[4,8]. Despite a history suggestive of claudication, many patients are handicapped by orthopaedic, pulmonary or cardiac disease and cannot walk on a treadmill. Other patients can only manage very short distances and cannot complete a one minute exercise test. Finally some patients who complain of claudication are limited on the treadmill by other factors.

To avoid these problems altogether attempts have been made to measure total limb or calf blood flow. It has been established that resting blood flow determinations are of no diagnostic value[9] and so blood flow measurements must be carried out after stress. Unfortunately the measurement of flow after exercise is technically difficult and simple pressure measurements correlate better with the maximum walking distance than do complex time-consuming flow measurements[9]. A compromise is to substitute the demands of reactive hyperaemia for the stress of exercise. Peak flow during the reactive hyperaemia that follows 3 min of arterial occlusion has proved efficient at discriminating between normal and diseased limbs[10].

Various methods of blood flow measurement have been used in the past, none of which is entirely satisfactory. Alternatives include ultrasonography[11,12] which may be used to estimate the mean flow in major arteries but does not take into account any collateral vessel formation. Radioisotopes have been used to study blood flow by measuring clearance rates of ^{99m}Tc pertechnetate following an intramuscular injection[13,14] and by first pass radionuclide arteriography[15]. Both methods have proved to be sensitive in detecting peripheral vascular disease but do not lend themselves to absolute measurements of flow.

The most commonly used technique is venous occlusion plethysmography employing either a volumetric[16] or gravimetric[17] technique. Unfortunately venous occlusion plethysmography has a poor signal to noise ratio at low flow rates, is subject to a variety of technical errors and artefacts[18] and uses equipment which is not widely available.

We have recently reported a new method for the measurement of limb blood flow that uses a radioactive isotope and a gamma camera[19]. A normal flow range has been established and its value in a series of clinical situations has been described[20]. The method has a high reproducibility even at low flow rates. The aim of this study was to evaluate isotope limb blood flow as a method of assessment of intermittent claudication, by comparison with other recognized techniques.

Patients and methods

Fifty-eight non-diabetic patients with a history suggestive of intermittent claudication were assessed. Twenty-five patients were excluded either because we could not reliably reproduce the symptoms of claudication on the treadmill, or if the maximum walking distance over the first two tests varied by more than 20 per cent. This left 33 patients (28 men, 5 women, mean age 63 years, range 41–79) who were entered into the study. Six patients were withdrawn after three treadmill tests as they began treatment which may have affected the results. This left 27 patients who had all four exercise tests. All 33 patients had a limb blood flow measurement carried out. Six patients had this repeated to confirm the reproducibility of the technique in this patient population.

Exercise tests were carried out according to the protocol shown in *Table 1*. They were conducted by the same observer in a controlled environment at an ambient temperature of 24°C. Observations were made at the same time each day and patients always wore the same footwear. Patients were asked to report the onset of pain, and this together with the maximum walking distance was recorded.

All systolic measurements were made with an Ultrasonic Doppler Flow Detector (model 811, Parks Medical Electronics, Inc., Beaverton, Oregon, USA). A blood pressure cuff was placed just proximal to the medial malleolus. The ankle–brachial systolic pressure index (Doppler ratio) was determined by dividing the highest of the posterior tibial or dorsalis pedis pressures by the highest brachial pressure. This was recorded for both legs at rest and for the most symptomatic leg immediately after the exercise test. The ratio was repeated at intervals until it had returned to normal. This is the recovery time. After a further 30 min rest period the post-hyperaemic ankle–brachial systolic pressure index was recorded. In order to be compatible with our method for isotope limb blood flow measurement this was carried out with two cuffs, one to record the ankle pressure, and the other placed just below the knee to produce 3 min of arterial occlusion.

The principles and method of isotope limb blood flow measurement have been described in detail elsewhere[19,20]. Briefly, the patient is placed supine with legs and feet over the field of view of a gamma camera. We have recently added a foot plate to the camera which ensures accurate positioning of the limbs and this has improved the reproducibility. The calves are isolated by rapidly inflating blood pressure cuffs placed immediately below the knee to a suprasystolic pressure. Isotope in the form of ^{99m}Tc labelled human serum albumin is then injected into the remaining blood pool via an antecubital fossa vein. A 3 min period of arterial occlusion allows equilibration of the isotope within the blood pool and produces the hyperaemic response. We have found that his period of occlusion is well tolerated by patients, even those with rest pain or severe claudication, and has not been associated with graft thrombosis. Following release of the cuffs the increasing activity within the limb is recorded by the gamma camera. By measuring the activity per unit volume of the labelled blood pool and the volume of the limb, flow per unit volume of tissue for the whole below knee segment can be calculated.

The results are expressed as means and standard deviations with ranges where indicated. Statistical analysis is by coefficient of variation and Pearson's linear regression.

Table 1 *Protocol for physical measurements*

Isotope limb blood flow measurement
4 exercise tests with a 2 week interval between each test
40 min pre-test rest period
Pre-test ankle–brachial systolic pressure index
A speed of 3 km/h and a 10° gradient
Pain-free and maximum walking distance recorded
Immediate post-exercise ankle–brachial systolic pressure index
Recovery time
Further 30 min rest period
Hyperaemic ankle–brachial systolic pressure index taken

Results

Physical measurements

Of the original 58 patients, 25 had to be excluded for a variety of reasons. Three proved too frail for exercise testing, six developed vertigo, four were limited by dyspnoea and two by angina. A further 10 had greater than 20 per cent variability between the first two treadmill tests and were also excluded. This left 33 patients who were entered into the study.

Examining the results for the 27 patients who had all four exercise tests (*Table 2*), the pain-free walking distance was an unhelpful measurement. Despite encouragement seven patients failed to report the onset of pain. In the 20 that did the mean pain-free walking distance was 50 m. The mean coefficient of variation for each patient between occasions was 19 per cent with some patients varying by over 50 per cent. Nevertheless, as a group there was a good agreement between tests with a highly significant r value of 0·9 ($P<0{\cdot}0001$).

In this same group of 27 patients the maximum walking distance was much more reliable. As with the pain-free walking distance there was a trend for the mean maximum walking distance to increase with time but this was not significant. This probably reflects the learning process. Over all four tests the mean maximum walking distance was 77·7 m and the mean coefficient of variation for each patient between occasions was 8 per cent. This is lower than for pain-free walking distance. Despite our initial exclusion of patients who performed poorly on a treadmill there were some whose coefficient of variation was as high as 31 per cent. Again the reproducibility between any two tests was good with an r value of 0·9 ($P<0{\cdot}0001$).

If we now consider the results for all 33 patients entered into the study (*Table 3*). There was a wide range of maximum walking distance. For all treadmill tests carried out the mean maximum walking distance was 70 m. This is lower than the mean for the group of 27 patients who had all four tests as the six patients who were withdrawn had severe claudication.

Many patients were hypertensive with a mean brachial pressure of 169 mmHg. The mean resting Doppler ratio for the symptomatic leg was 0·61 and the reproducibility of this measurement was 0·81 ($P<0{\cdot}0001$). Some patients had symptoms of claudication with only minimally reduced ratios

Table 3 *Results for all 33 patients*

	Mean ± s.d.	Range
LBF (symptomatic leg)*	4·2 ± 1·9	1·8–10·5
LBF (asymptomatic leg)*	7·8 ± 3·3	3·5–15·1
Maximum walking distance (m)	70 ± 60	12–335
Brachial pressure (mmHg)	169 ± 35	120–235
Doppler ratio (symptomatic leg)	0·61 ± 0·17	0·3–0·9
Doppler ratio (asymptomatic leg)	0·89 ± 0·21	0·4–1·2
Post-exercise Doppler ratio	0·2 ± 0·2	0·0–0·8
Recovery time (min)	11·4 ± 8·4	2·0–30·0
Post-hyperaemic Doppler ratio	0·2 ± 0·2	0·0–0·7

* Limb blood flow (LBF) expressed as ml/100 ml of tissue/min

Table 2 *Treadmill results for 27 patients who had four exercise tests*

	Pain-free walking distance (m)	Maximum walking distance (m)
n	20*	27
Occasion 1	47·8 ± 30·0	76·5 ± 42·5
Occasion 2	49·6 ± 35·6	77·4 ± 44·1
Occasion 3	49·6 ± 31·9	77·5 ± 45·1
Occasion 4	53·8 ± 30·0	79·3 ± 43·8
Mean coefficient of variation	19% (range 6–55%)	8% (range 3–31%)
Reproducibility (between any two tests)	0·9	0·9

* Seven patients failed to report the onset of pain

Table 4 *Correlation between tests*

	r	P
Maximum walking distance and:		
Limb blood flow	0·35	0·02
Resting Doppler ratio	0·09	0·31
Post-exercise Doppler ratio	0·14	0·10
Recovery time	0·34	0·03
Hyperaemic Doppler ratio	0·14	0·22
Limb blood flow and:		
Resting Doppler ratio ($n = 66$)	0·69	< 0·0001
Post-exercise Doppler ratio	0·41	0·01
Recovery time	0·35	0·02
Hyperaemic Doppler ratio	0·58	0·0005

but all these patients had a reduced limb blood flow. Despite the lack of significant symptoms the ratio was often markedly reduced in the asymptomatic leg, the mean was 0·89 with results ranging from 0·4 to 1·2.

Both exercise and ischaemia produced a consistent fall in the Doppler ratio. The mean post-exercise and post-hyperaemic Doppler ratios were both 0·2. There was good agreement between the two ($r = 0·5$). Recovery time varied considerably (range 2–30 min) with a mean time of 11 min.

The mean limb blood flow to the symptomatic leg was 4·2 ± 1·9 ml/100 ml of tissue/min. There was a wide range of flow values obtained and some patients suffered claudication despite a relatively high total limb blood flow. The mean limb blood flow to the asymptomatic leg was 7·8 ml/100 ml of tissue/min. Indeed only 12 patients had flows to their asymptomatic leg above 10 ml/100 ml of tissue/min, a value that probably represents the lower end of the normal range for this technique. For the six patients within this group who had the test performed twice the correlation was 0·97. This is consistent with our previous experience with a large group of claudicants and normal controls.

Correlations

To establish the value of the physical tests in the assessment of intermittent claudication we attempted to correlate the maximum walking distance and the limb blood flow with the other measurements (*Table 4*).

Only limb blood flow and recovery time correlated significantly with maximum walking distance with r values of 0·35 and 0·34 respectively. None of the other tests bore any relationship to the maximum walking distance. In particular the correlation between the resting Doppler ratio and the maximum walking distance was very poor ($r = 0·09$).

The limb blood flow showed a significant correlation with all Doppler ratio measurements and the recovery time. It should be noted that only the resting Doppler ratio and the limb blood flow was available for both legs of each patient and so $n = 66$.

Discussion

There is no doubt that treadmill testing is the most physiological assessment of intermittent claudication, but there are several practical difficulties[21]. Despite calls for standardization at recent international meetings there remains no accepted protocol for carrying out such tests. Both Laing and Walker have suggested a treadmill speed of 4 km/h on a 10° slope and Laing has compared this with a speed of 6 km/h[4,8]. Previous experience has shown that this is too fast for our patient population. This has been confirmed in this study. Even at our chosen speed of 3 km/h 15 out of 58 patients could not manage the test.

The disadvantages of treadmill tests are that they do not reproduce normal walking, rely on an end-point determined by the patient, and are associated with a high incidence of electrocardiographic abnormalities[22]. In addition some patients whose walking is restricted by claudication are limited on the treadmill by factors other than claudication, which makes their assessment using this test impossible. This applied to over one-quarter of our original 58 patients, which is comparable to that found in other studies[22]. If the results of treatment in this group are to be assessed an alternative test is required.

Attempts to remove the subjectivity of treadmill tests by adopting a one minute exercise period and measuring the fall in ankle systolic pressure. and the recovery time, have been suggested by both Laing and Walker[4,8]. This does not resolve the problem posed by those patients who cannot walk on a treadmill. In addition, even at a speed of 3 km/h, 12 of our 33 patients could not walk on the treadmill for one minute. We would estimate that a 4 km/h, one minute exercise test, could be applied to less than half our patient population. Therefore we have returned to the simple recording of pain-free and maximum walking distances.

We agree with Berglund that of these two subjective measurements the maximum walking distance is the more reproducible[7]. In contrast to his results we found both tests to have a highly significant reproducibility of 0·9. This would suggest that they are satisfactory measures of claudication for those patients who can walk on a treadmill.

We have found the reproducibility of resting Doppler ratios between successive occasions to be 0·81. Despite this there was no correlation with the maximum walking distance. This is not surprising but we note that Yao has found a correlation between these tests of 0·44[23]. In Yao's study, the treadmill exercise test was terminated at 5 min even if the patient had not noticed any pain. Many patients had not walked to their maximum distance and this may have been responsible for a spuriously high correlation.

Others have found that the addition of stress, either exercise or arterial occlusion[4] improves the specificity of Doppler measurements. We found only a minimal improvement in the correlation obtained with the resting Doppler ratio after the addition of either form of stress. Verhagen has demonstrated an excellent correlation between the Doppler index obtained immediately after exercise and that obtained during post-occlusive reactive hyperaemia in a large series[6]. In our smaller series we found a significant correlation between these measurements of 0·5. The advantage of the Doppler ratio during reactive hyperaemia is that it can be applied to those patients who cannot walk on a treadmill and is entirely objective.

The recovery time is a function of the work done and this has been well demonstrated by Laing who compared the effect of various exercise times and rates on ankle systolic pressure[8]. The recovery times gave a correlation with maximum walking distance of 0·34. The ratio of maximum walking distance and limb blood flow gives an indication of the degree of exertion and if this is compared with the recovery time then a more significant correlation is obtained ($r = 0·6$).

The alternative to measurement of systolic pressure after stressing the circulation is to measure limb blood flow under the same circumstances. The measurement of flow following exercise is technically difficult. To overcome this Clement has measured flow following arterial occlusion using venous occlusion plethysmography and found peak flow during the hyperaemic phase to be a good indicator of disease[10].

Our technique of isotope limb blood flow measurement also defines flow during this phase. Both this and venous occlusion plethysmography can be applied to any patient, despite any physical handicaps they may suffer, as neither relies on treadmill testing. Our technique is not subject to many of the disadvantages of venous occlusion plethysmography. In particular it has a very high reproducibility, a high signal to noise ratio even at low flow rates and uses equipment which is already available at many hospitals.

When planning treatment it is important to have information about both limbs. Laing reports that 45 per cent of 58 apparently asymptomatic limbs proved functionally abnormal following a one minute exercise test[8]. In only 14 per cent was the abnormality detected by the resting Doppler ratio alone. In 31 asymptomatic limbs in our series, 58 per cent had a resting Doppler ratio below 0·9, but 71 per cent had an abnormal limb blood flow. Four patients had an abnormal limb blood flow despite a normal resting Doppler ratio. These results emphasize the danger of relying on tests of intermittent claudication that are insensitive and only provide information about one leg.

We were not surprised at the relatively low but significant correlation between maximum walking distance and the limb blood flow to the symptomatic leg. Maximum walking distance is a subjective assessment and may not represent the maximum exercise capability of the limb. In addition, in some patients an abnormal distribution of flow may produce claudication despite a relatively high total blood flow. We are investigating this further by an extension of the technique which defines regional flow. These factors, together with the variation in cardiorespiratory capacity between patients, may explain the wide flow range obtained. Refinement in segmental flow measurement may be valuable in the prediction of amputation healing.

The value of any new technique must be judged on its ability to assess and influence treatment. We have used isotope limb blood flow measurements to assess the results of vasodilator therapy, angioplasty and to predict amputation healing. We have reported early results using the technique to assess arterial bypass graft function[24] and have found that the changes in blood flow following surgery correlate well with clinical outcome. We are currently evaluating vasodilator therapy, angioplasty, sympathectomy and arterial bypass grafting in a prospective manner.

One advantage of the technique is that it utilizes equipment that is already available in many hospitals. The test is carried out by one medical physicist and a radiographer and takes 20 min to perform. We have found that batching studies in groups of four to a session is both cost-effective and efficient. The isotopes and syringes are the only disposables needed, each test costs less than £15.

To conclude, treadmill testing is the most physiological method of assessment for intermittent claudication but cannot be applied to every patient. Isotope limb blood flow provides an alternative that is reproducible and has the advantage of providing an equally accurate flow measurement for both legs. The test is simple to perform, and can be recommended for the minimally invasive assessment of intermittent claudication.

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Br. J. Surg. 1987, Vol. 74, June,
520–522

Effect of pre-operative blood transfusion on tumour metastases

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The effects of allogeneic blood transfusion on the subcutaneous growth and metastatic spread of two types of mouse tumour (B16 melanoma syngeneic to the C57/BL6 mouse and UV-2237 fibrosarcoma syngeneic to the C3H/He mouse) were studied. The growth rates of the primary tumour were not altered by transfusing the animals with allogeneic blood 14 days before tumour inoculation, but spontaneous metastasis from tumours formed at the inoculation site was augmented and accelerated for both tumour types. This effect was dependent on the strain of the blood donor, metastases of B16 melanoma being augmented by transfusion with blood from Balb/c animals, and UV-2237 fibrosarcoma by transfusion with C57/BL6 blood, but not by blood from other donor strains tested.

Keywords: Blood transfusion, tumour, metastases

The beneficial effect of blood transfusion in prolonging renal allograft survival was first noted in the early 1970s[1] and routine, elective transfusion of patients awaiting transplantation is now established practice in many centres. The precise mechanisms involved in reducing graft rejection by this means are not yet known despite extensive clinical and experimental research[2,3].

Patients with cancer undergoing surgery frequently receive perioperative blood transfusion. If immunological mechanisms contribute to the limitation of tumour growth and spread, there is a possibility that prognosis could be adversely affected in transfused patients. Several recent retrospective clinical studies have found evidence to support this theoretical concept[4–6] but experimental study of this topic is less extensive and has yielded conflicting results[7–9]. Published work has focused mainly on the growth rate of implanted tumours in transfused animals and none has investigated the effect of blood transfusion on tumour metastases.

The potential of tumours to spread or recur confers on the tumour cell population the ability to survive excision of the primary. As cancer patients are frequently anaemic, perioperative blood transfusion is often difficult to avoid. However, as this could have important risks for health and survival, this investigation of the effect of allogeneic transfusion on the spread of two types of mouse was undertaken.

Materials and methods

Animals

Female C57/BL6, C3H/He and Balb/c mice aged 6–8 weeks (Olac Ltd.) were used in these experiments.

Tumour cell lines

Studies were conducted on two tumour cell lines. B16-F10-B2 (syngeneic to C57/BL6 mice) and UV-2237-IP3 (syngeneic to C3H/He mice). These were maintained in monolayer cell culture in Minimal Essential Medium (Gibco) supplemented with 10% fetal calf serum and antibiotics. When confluent monolayers were obtained the cells were harvested with 0·025 per cent trypsin/EDTA and their viability assessed using fluorescein diacetate staining[10]. Both tumour lines were spontaneously metastatic from the subcutaneous site to the lungs.

Experimental protocol

The transfusion protocol in this study was based on previous work investigating the prolongation of mouse allograft survival by allogeneic blood transfusion. The volume of blood and the timing of the transfusion were those that produced the longest graft survival times.

Whole blood

Groups of mice used in these experiments were transfused via the lateral tail vein with 0·25 ml of either normal saline or syngeneic blood (control groups), or with allogeneic blood (experimental groups). In the experimental groups, C57/BL6 animals were transfused with Balb/c or C3H/He blood, and C3H/He animals with Balb/c or C57/BL6 blood. Fourteen days later tumour cells were inoculated subcutaneously into groups of syngeneic animals: $0\cdot5 \times 10^6$ B16-F10 cells into C57/BL6 mice and 10^6 UV-2237 cells into C3H/He mice.

Lymphocytes

In order to investigate the effect of transfused lymphocytes on tumour growth and metastases, cells were prepared from both peripheral blood and spleen. Blood was diluted with culture medium and layered onto Lymphoprep (Nycomed UK Ltd.). Centrifugation at 3000r.p.m. for 20 min resulted in a mononuclear cell band at the interface between the Lymphoprep and the culture medium. The cells were washed, counted and resuspended for IV inoculation. To prepare splenic lymphocytes, spleens were teased apart in culture medium and then filtered to obtain a single cell suspension. Red cells were lysed with water and the cells were then washed, counted and resuspended in culture medium.

C3H/He mice were injected intravenously with 10^6 C57/BL6 lymphocytes from either blood or spleen and 14 days later these animals were inoculated SC with UV-2237 fibrosarcoma cells. C57/BL6 mice were injected with 10^6 Balb/c splenocytes and subsequently inoculated SC with B16 melanoma cells.

Data collection

Tumour growth in all animals was monitored weekly by measurement of two transverse tumour diameters with calipers. When animals died, or were killed, full autopsies were performed and histological sections of all solid parenchymal organs assessed independently by two observers.

Statistical analysis

Statistical analysis was performed using Fisher's exact test.

Results

Tumour volume

Figures 1 and *2* show the increases in tumour volume after tumour cell inoculation. There was no significant alteration in tumour growth in animals which were pretransfused with allogeneic blood compared with those transfused with either syngeneic blood or saline.

Spontaneous metastases

B16-F10 tumour cells. After 21 days, 16 control animals had no evidence of macroscopic lung secondaries from tumours formed subcutaneously on the back (*Table 1*). Serial sections of the lung at multiple levels showed no evidence of microscopic tumour foci. However, those animals transfused with either Balb/c whole blood or splenocyte 14 days before the inoculation of the same number of tumour cells had multiple tumour deposits within the lungs in 5/6 animals in each group at 21 days,

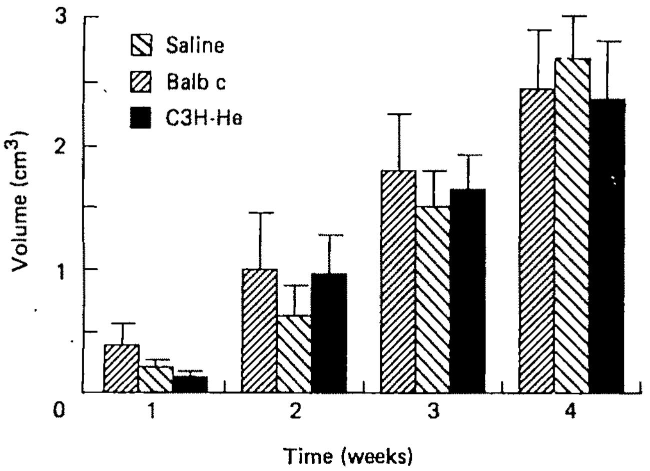

Figure 1 *Growth of B16-F10 tumours in mice transfused with saline, Balb/c or C3H/He blood. Values shown are mean volume (cm³) and s.d.*

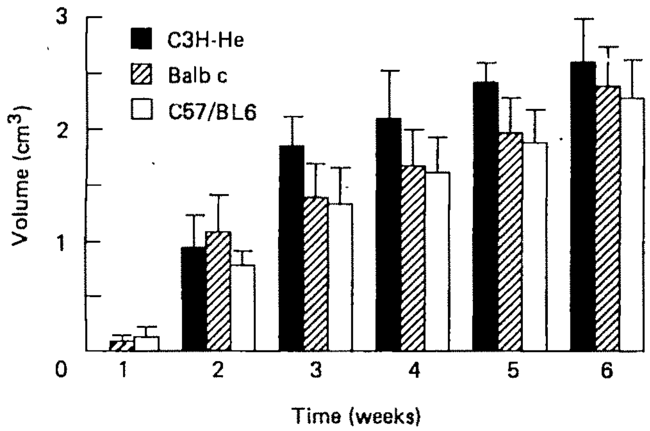

Figure 2 *Bar chart showing the growth of UV-2237 tumours in mice transfused with syngeneic (C3H/He), Balb/c or C57/BL6 blood. Values shown are mean volumes (cm³) and s.d.*

and the histology of the lesions were compatible with multiple secondary deposits rather than primary lung tumours. These increases in the incidence of spontaneous metastases were significant when compared with the control groups ($P<0\cdot01$). Transfusion with C3H/He blood, however, did not have the same effect.

UV-2237 tumour cells. Ten control animals (transfused with normal saline) were killed at 28 days and none had either macroscopic or microscopic evidence of metastases in the lungs from the primary sites on the back (*Table 2*). However, at 28 days mice transfused with either Balb/c or C57/BL6 blood 14 days before tumour inoculation had histologically proven metastases in 2/6 and 4/6 animals respectively.

In a further experiment, animals inoculated with the same number of UV-2237 tumour cells were allowed to survive for 56 days (*Table 2*). In this group two out of ten control animals had developed single lung metastases, but all the animals (6/6) transfused with C57/BL6 blood had developed multiple macroscopic lung secondaries at 56 days, which was a significant increase ($P<0\cdot01$). A similar augmentation in spontaneous metastases was seen in those animals transfused with either C57/BL6 peripheral blood lymphocytes or splenocytes. Cumulatively metastasis was therefore seen in 19/24 animals transfused with blood or lymphocytes, compared with only 2/10 controls.

In summary, transfusing groups of mice with allogeneic blood had no effect on the growth rate of the primary tumours, but the spontaneous metastasis of both tumour types was augmented and accelerated by transfusion with whole blood or lymphocytes from certain strains.

Discussion

Many clinical studies have found a positive association between perioperative blood transfusion and a worsening in prognosis in cancer patients, as defined by either a decrease in 5 year survival or an increase in local recurrence rates[4–6].

These reports have taken into consideration other factors known to be related to prognosis, for example tumour stage and pathological grade, and also factors which may have influenced the decision to transfuse the patient such as pre-operative haemoglobin, length of operation, tumour fixity and peroperative blood loss. It is noted, however, that although the majority of studies concur on these findings there are exceptions[11].

Experiments on murine tumour systems using differing transfusion protocols have yielded conflicting results. Most of the studies have investigated the effect of transfusion on the growth of the primary tumour, with some reporting an acceleration of tumorigenicity in animals transfused with allogeneic blood[8,9], whilst others showed no such effect[7]. However, as far as we know there has been no previous demonstration of an increase in the incidence of spontaneous metastases from a primary subcutaneous tumour following blood transfusion as demonstrated in this report.

Metastases were also augmented in this study by treating the animals with lymphocytes from either peripheral blood or the spleen. Preliminary data show no evidence of acceleration of tumour spread in C57/BL6 mice bearing B16 melanomas when these animals were transfused with Balb/c serum, and only a moderate acceleration when animals were injected with Balb/c red cells (3/6 animals) which may have been secondary to mononuclear cell contamination of the preparation. Similar findings have been reported from studies of accelerated Lewis lung carcinoma growth by blood transfusion[12], and the beneficial effect of prolonging organ allograft survival in animal

Table 1 *Animals with B16-F10 lung metastases 21 days after tumour inoculation, previously transfused with saline, syngeneic blood, allogeneic blood or allogeneic splenocytes*

Transfusion	No. animals	No. animals with metastases
Controls		
Saline	10	0/10 lung metastases
C57/BL6 blood	6	0/6 lung metastases
Experimental groups		
C3H/He blood	10	1/10 lung metastases
Balb/c blood	6	5/6* lung metastases
Balb/c splenocytes	6	5/6* lung metastases

* $P<0\cdot01$ (Fisher's exact test)

Table 2 *Animals with UV-2237 lung metastases (a) 28 days and (b) 56 days after tumour inoculation, previously transfused with either saline, allogeneic blood or allogeneic lymphocytes*

		No. animals with lung metastases	
Transfusion	*n*	(a) 28 days	(b) 56 days
Controls			
Saline	10	0/10	2/10
Experimental groups			
Balb/c blood	6	2/6	3/6
C57/BL6 blood	6	4/6**	6/6**
C57/BL6 splenocytes	6	—	5/6*
C57/BL6 blood lymphocytes	6	—	5/6*

** $P<0\cdot01$, * $P<0\cdot02$ (Fisher's exact test) systems has also been shown to be related to the lymphocyte population[3]. On the basis of this experimental evidence clinical trials have been suggested to investigate the possible benefit of using washed red cells rather than whole blood for patients with tumours.

The mechanism of this stimulatory effect of blood transfusion on metastasis cannot be deduced from the information so far obtained. However, blood transfusion is known to have suppressive effects on the host immune system and decreases in T lymphocyte helper/suppressor ratios[13,14], natural killer (NK) cells[13,15], and antibody production[16] have all been reported. Furthermore it is known that patients with solid tumours have abnormal responses to tests of immune provocation[17], while surgery and general anaesthesia have also been documented as causing immune suppression[18]. It is therefore possible that a number of mechanisms may contribute to the impaired immunological status of the host and hence to the understanding of the reported effects of blood transfusion on tumour behaviour.

Any correlation between this experimental work and the studies on human tumour growth and behaviour after transfusion must obviously be circumspect. The clinical studies have predominantly investigated colorectal tumours which are not strongly immunogenic, and it is therefore possible that different mechanisms may explain the effects reported to be associated with perioperative transfusion of humans with cancer. It is also likely that the intensity of any immunosurveillance exercised by the host against disseminating tumour cells is related to the individual tumour and differs between species. The concept of control of tumour development by immunosurveillance mechanisms has been challenged on the grounds that T cell deficient animals do not have an increased incidence of spontaneously occurring tumours other than those produced by DNA viruses. However, abrogation of metastatic behaviour in a syngeneic tumour system by transfection of histocompatibility (MHC) genes has recently been reported[19], implying that immunosurveillance mechanisms can, in some tumour systems, affect tumour progression.

The degree of lung colonization following intravenous inoculation of the B16-F10 and the UV-2237 tumours is known to be inversely related to the levels of host NK activity present within the spleen[20]. Other studies have provided evidence indicating that cells from lung metastases are more resistant to NK lysis than cells from the primary tumour[21], and that *in vitro* selection of NK resistant tumour cells is accompanied by an increase in the metastatic capacity of the cells *in vivo*[22]. The increase in spontaneous metastases reported here may therefore be due to a decrease in NK cell activity secondary to blood transfusion, allowing blood borne metastases to colonize the lung, whereas in control groups these cells were destroyed. It is worth comment that these studies have all been conducted in mouse tumour models, whereas solid human tumours contain numerous NK resistant cells. However, the critical targets for NK cell lysis in a tumour are the stem cells and recent studies in human adult leukaemias have shown that NK cells can significantly inhibit clonogenesis[23].

Although there are similarities in the clinical effects of blood transfusion in cancer patients and the observations made in this study, direct extrapolation is not possible as the mechanisms in the two species may be different. This will only become apparent from further investigations in both systems.

Acknowledgement

This work was supported by the Anthony Placito Memorial Fellowship Fund.

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Br. J. Surg. 1987, Vol. 74, June, 523–525

Inhibition of intestinal carcinogenesis by dietary supplementation with calcium

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Dietary supplementation with calcium reduces colonic crypt cell production rates in both normal and hyperplastic mucosa. Calcium can bind intraluminally with bile salts and fatty acids thus reducing their mitogenic effect. The protective role of oral calcium on intestinal carcinogenesis (induced by azoxymethane) was tested in 60 male Sprague–Dawley rats submitted to either 80 per cent mid jejuno-ileal resection (n = 30) or jejunal transection (n = 30). Half the rats in each group received calcium lactate 24 g/l added to their drinking water. Rats were killed 25–27 weeks postoperatively. Enterectomy increased colonic tumour yield by 60–106 per cent (P = 0·002–0·005) and duodenal tumour yield by 70–86 per cent. Calcium abolished this effect at both sites, halving intestinal tumour yields in rats with both transection and resection (P < 0·05). Doubling the dietary intake of calcium inhibits experimental carcinogenesis.

Keywords: Calcium, colonic tumours, small bowel resection, duodenal tumours, azoxymethane

Dietary supplementation with a modest dose of calcium lowers the epithelial cell proliferation rate in colonic crypts of individuals susceptible to colorectal cancer[1]. Calcium probably acts by binding to bile acids and fatty acids so reducing their mitogenic effects[2]. Bile acids are potent promoters of experimental colonic carcinogenesis[3] and might have a similar role in man[4,5]; their harmful effect can be reduced by intraluminal metronidazole[3] or calcium[6].

We have recently shown that doubling the oral intake of calcium nearly halves crypt cell production rate in rat descending colon and abolishes the adaptive response to enterectomy[7]. The present study was designed to examine its protective effect on azoxymethane-induced intestinal carcinogenesis. Since intestinal hyperplasia resulting from surgical or other manoeuvres predisposes to neoplasia[8], the effect of calcium was studied in both normal and adapting epithelium.

Materials and methods

Experimental design

Sixty male Sprague–Dawley rats weighing 150 ± 14 g (mean ± s.e.m.) were admitted to the animal house one week before the start of the experiment and were allocated to one of four groups. Azoxymethane was diluted on receipt from the manufacturers (Ash Stevens Inc., Detroit, Michigan, USA) and stored at −20°C. Aliquots were subsequently thawed as required and further diluted before injection. All rats received 6 SC injections of azoxymethane (15 mg kg^{-1} $week^{-1}$). Two to five days after the last injection, rats (now weighing 343 ± 36 g) were submitted to laparotomy under light ether anaesthesia. Half the animals had an 80 per cent mid-enterectomy with end-to-end anastomosis between proximal jejunum and distal ileum. The other half had transection of the jejunum at a point 10 per cent along the length of the small bowel from the ligament of Treitz. Half the animals in each group received calcium lactate (24 g/l), which was added to the drinking water from the first postoperative day until the conclusion of the experiment. This was the same dose of calcium lactate that had a clear-cut antitropic effect in the previous experiment[7]. It approximately doubles the rats' daily intake of calcium. As before it was well tolerated and did not affect water consumption.

To prevent postoperative bleeding previously found to be troublesome in this strain of rat, vitamin K_1 0·25 mg/kg IM was given at the end of each operation. Four animals died in the early postoperative period and another three from intestinal obstruction during the sixth postoperative week.

Intestinal tumours

All rats were killed 25–27 weeks following the initial dose of azoxymethane or earlier if distressed or moribund. A specimen of blood was taken by cardiac puncture. The entire intestinal tract was excised, gently washed in cold saline and scrutinized for evidence of neoplasia. Tumours and suspected tumours were fixed in 10 per cent formalin, and the tissue was subsequently embedded in paraffin. Sections 5 μm thick were cut and were stained with haematoxylin and eosin for histological examination. The tumours were classified according to Sunter and colleagues[9].

1. Adenoma.
2. Group 1 carcinoma: an early invasive adenocarcinoma arising in an adenoma but penetrating the muscularis mucosae.
3. Group 2 carcinoma: a frankly invasive carcinoma moderately or well differentiated with residual evidence of a likely origin from an adenoma.
4. Group 3 carcinoma: carcinomas with predominant mucin secretion, signet ring cells or very poor differentiation.

Statistics

An analysis of variance (the Kruskal–Wallis test) was used initially to compare all four groups. Tumour yields were subsequently compared using the Mann–Whitney *U* test. Body weight and serum calcium were compared using Student's *t* test.

Results

Mortality rate

Six rats (10 per cent) died between weeks 22 and 25, two each from obstructing cancers of the duodenum and one each from metastatic colon cancer and cancer of the external auditory canal. These animals were included among those analysed for overall tumour yield, numbers of which are shown in *Table 1*.

Table 1 *Body weight at death*

Group	*n*	Weight (g)
80% SBR + added calcium	13	525 ± 54
80% SBR alone	15	518 ± 60
Transection + added calcium	11	543 ± 49
Transection alone	14	560 ± 59

SBR, small bowel resection

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Table 2 *Serum levels of calcium*

Group	*n*	Calcium (mmol/l)
80% SBR + added calcium	13	2·88 ± 0·18
80% SBR alone	15	2·75 ± 0·18
Transection + added calcium	11	2·94 ± 0·20
Transection alone	14	2·79 ± 0·12

SBR, small bowel resection

Table 3 *Duodenal tumours*

	n	Median	Total
80% SBR + added calcium	13	0	6
80% SBR alone	15	1	14*
Transection + added calcium	11	0	3
Transection alone	14	1	7*†

SBR, small bowel resection
* $P<0{\cdot}05$ *versus* equivalent group receiving added calcium; † $P<0{\cdot}05$ *versus* group with 80 per cent SBR alone

Body weight

Rats in all four groups gained weight steadily until 18 weeks postoperatively, when weight reached a plateau for 6 weeks and then slowly began to decline. At death there was no difference in weight between calcium and non-calcium groups. Although small bowel resection was associated with a lower body weight (3–8 per cent), this difference did not attain statistical significance (*Table 1*).

Serum calcium

There were no significant differences in levels of serum calcium at death between any of the four groups (*Table 2*).

Duodenal tumours

Although the overall yield of duodenal tumours was < 1 per rat, supplemental calcium reduced their incidence by 46 per cent in rats with transection and by 51 per cent in rats with resection (*Table 3*). Mid small bowel resection nearly doubled duodenal tumour yields, but this difference was only significant in groups not receiving calcium.

Colorectal tumours

Extensive small bowel resection increased colorectal tumour yields by 60 per cent in controls and by 106 per cent in rats with added calcium, when compared with values in transection animals (*Figure 1*). Calcium supplements halved the yield both in rats with transection (4·3 to 1·8 tumours/rat) and in rats with resection of the intestine (6·9 to 3·7 tumours/rat). The proportion of malignant colonic neoplasms was similar in all four groups (56–67 per cent), but in rats taking added calcium there were relatively few early malignant (type 1) lesions; the number of more advanced malignancies (types 2 and 3) was similar in non-calcium and calcium-treated animals (*Figure 2*).

Discussion

These results show that calcium inhibits chemical carcinogenesis in the colon and duodenum. We confirm previous work showing increased numbers of large bowel cancers following jejuno-ileal bypass[10] and increased numbers of duodenal cancers following subtotal enterectomy[11]. In a parallel experiment examining the effect of calcium on colonic crypt cell production rates (CCPR)[7], we showed that calcium was antitropic to both normal and hyperplastic colonic mucosa. Tumour yields in the present experiment correlate with the previous CCPR data and demonstrate a further link in the adaptation–carcinogenesis sequence[12].

Our previous finding that calcium lactate 24 g/l caused a slight increase in serum calcium[7] was not confirmed in the present experiment and is thus in agreement with Holt and colleagues who showed little variation in calcium absorption in diets containing excess calcium[13]. Since calcium alters the luminal but not the systemic milieu, it seems unlikely that oral supplements could change the mode of action of a parenterally administered carcinogen. However manoeuvres that cause colonic hypoplasia (e.g. colostomy) are known to reduce colonic neoplasia[14]. Calcium specifically reduced the incidence of Type 1 (early) malignant neoplasms, without altering the numbers of benign tumours or advanced cancers. It therefore appears to act at an early stage in the evolution of colorectal carcinoma, possibly owing to a general stabilizing influence on mucosal proliferation.

The antitropic and anti-cancer actions of calcium may reflect its ability to bind bile acids and fatty acids as calcium soaps in the lumen of the bowel thus rendering them non-irritative to colonic mucosa[2]. Epidemiological studies suggest a correlation between the incidence of large bowel cancer and the total dietary fat intake[15], and high fat diets increase faecal excretion of bile acids[16,17]. High fat diets also promote experimental colonic

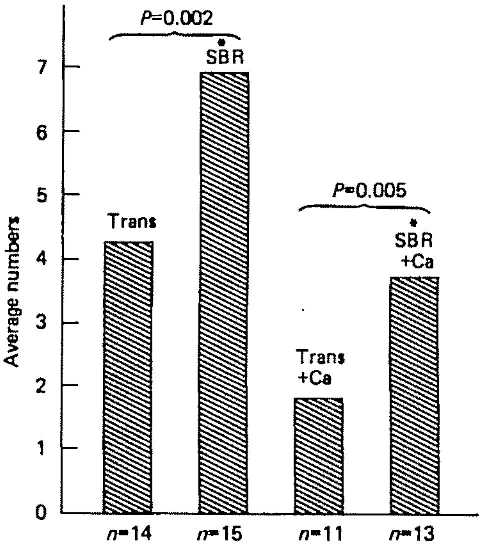

Figure 1 *Number of colorectal tumours per rat (mean values are shown). Trans, transection; SBR, small bowel resection; Ca, calcium.* * $P<0{\cdot}001$ versus *equivalent groups receiving added calcium*

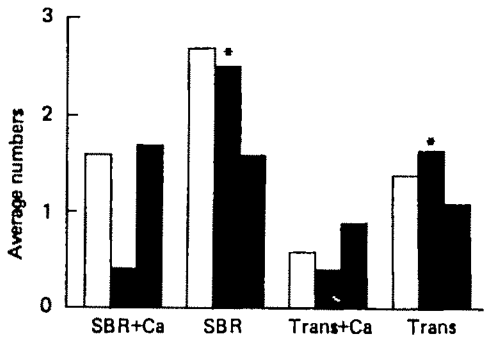

Figure 2 *Classification of colorectal tumours. Mean number of tumours of each type shown. Trans, transection; SBR, small bowel resection; Ca, calcium.* □, *Benign;* ■, *malignant (1);* ■, *malignant (2+3).* * $P<0{\cdot}01$ versus *equivalent groups receiving added calcium*

neoplasia[17], and bile acids have a similar effect whether given by mouth[18] or per rectum[3]. It has been known for over 60 years that faecal fat excretion is influenced by the amount of calcium soap formation[19,20]. Calcium-enriched diets lead to decreased fat absorption because of soap formation[21]. Thus by binding with fat in the upper intestine calcium may reduce the levels of harmful bile acids. However fatty acids have also been shown to be toxic to the distal colon if instilled locally[22], so that calcium might also work by reducing mucosal damage and the concomitant proliferative stimulus[22].

Doubling the dietary calcium halved the yield of duodenal tumours. Although duodenal cancer is rare in man, duodenogastric reflux of bile has been implicated in gastric carcinogenesis[23]. Conceivably calcium could protect against gastric mucosal damage (and thus cancer) in the stomach as it does in the large intestine[6].

The strong potentiating effect of 80 per cent small bowel resection on carcinogenesis is completely negated by doubling the oral intake of calcium. Subjects with a high risk of developing colonic carcinoma have an increased proliferative rate in colonic crypts maintained in organ culture, but rates can be restored to normal simply by doubling the daily intake of calcium[1]. The close link between hyperplasia and neoplasia of the intestine in animals[8] may also apply to man. Patients with ulcerative proctocolitis have increased CCPR in cultured rectal biopsies[23] and have a well-established predisposition to cancer. Likewise colonic anastomoses are sites of intense proliferative activity[25], and suture-line carcinomas are common after resection of the large bowel[26]. A recently completed 19 year study showed that the risk of acquiring colorectal cancer was inversely correlated with dietary calcium and vitamin D[27]. It is therefore plausible that by taking a small oral dose of a calcium salt the incidence of colorectal cancer could be lowered in man. The normal adult intake of calcium is 1 g/day. A further 1–2 g per day should certainly be harmless and might have additional benefits. Up to 33·5 g calcium daily has been taken without adverse effect[21], and calcium may lower serum lipids[28] and reduce diastolic blood pressure[29].

Acknowledgements

We thank Dr P. Quirke for help in the preparation and reporting of the histological sections.

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Surgical Research Society Abstracts

Br. J. Surg. 1987, Vol. 74, June, 526–548

Hormonal responses of intra-portal islet autografts in the cynomolgus monkey

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Isolated islets of Langerhans obtained from a single donor pancreas by a recently described technique have been shown to restore fasting normoglycaemia after total pancreatectomy in the cynomolgus monkey[1]. We report the first detailed metabolic studies of islet graft function in monkeys. Five animals underwent total pancreatectomy and intraportal islet autografting. After 3 months intravenous bolus (500 mg kg^{-1}, G-bolus) and low-dose continuous (12·5 mg kg^{-1} min^{-1}, G-infused) infusions of glucose and L-arginine (12·5 mg kg^{-1} min^{-1}, A-infused) were given to these five animals, and to four normal animals. Plasma glucose, insulin and glucagon levels were measured at regular intervals during each infusion and geometric means calculated (*Table*).

	Glucose (mmol/l)		Insulin (milliunits/l)		Glucagon (ng/l)	
	†Δ2 min	60 min	†Δ2 min	60 min	†Δ2 min	60 min
G-bolus controls	10·3	2·3	79·2	18·8	−31·5	*76·5
G-bolus transplants	10·3	4·1	31·7	21·7	−18·1	*26·9
G-infused controls	0·9	11·0	10·3	65·1	−34·6	***52·7
G-infused transplants	1·8	10·8	19·1	49·4	−1·6	***6·4
A-infused controls	0·1	2·9	14·4	13·2	128·7	**721·7
A-infused transplants	0·1	2·7	8·3	11·1	87·3	**135·3

† change from fasting values; $^{*}P<0{\cdot}05$; $^{**}P<0{\cdot}02$; $^{***}P<0{\cdot}001$; unpaired t test

The insulin responses to either a glucose bolus or a continuous infusion of glucose in transplanted animals were qualitatively similar to those in normal animals, In all animals glucagon levels fell after intravenous glucose and rose during L-arginine infusion, but the levels attained were significantly lower in transplanted animals. These results suggest that qualitatively normal hormonal responses may be obtained in a diabetic recipient by isolated transplantation from a single donor pancreas.

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Atheroma—a new hypothesis

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A recent hypothesis[1] has suggested that the key event in the development of the early plaque in atheroma may be the abnormal proliferation of smooth muscle cells (SMC). It is suggested that this is regulated by release of a number of growth modulatory polypeptides, including platelet derived growth factor (PDGF), which can potentially originate from platelets, endothelial cells and macrophages. In this paper we present evidence that human SMC themselves secrete a growth factor-like molecule which regulates this proliferation.

We isolated several SMC lines from various samples of human aorta, and examined them for both the production of PDGF-like proteins, and for the possible activation of the PDGF A-chain and B-chain genes. Several such lines continued to secrete a growth factor into serum-free medium after 40 days in culture. Parallel experiments using Northern blot analysis unexpectedly revealed the activation of the PDGF A-chain gene in all lines examined.

These data raise the possibility that vascular damage may activate the gene encoding one of the polypeptide chains of PDGF in adjacent SMC. Such cells might then, after migration, become capable of autonomous growth in an analogous manner to cells transformed by Simian Sarcoma Virus, whose *cis* oncogene encodes the B-chain of PDGF.

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The prognostic value of simultaneously-evaluated assays of neutrophil function and lymphocyte subset ratios in burns

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Investigators disagree on the prognostic significance of alterations in neutrophil chemotaxis and bactericidal capacity following burns[1] and, although lymphokines produced by helper (T4) and suppressor (T8) T lymphocytes profoundly influence these functions[2], the relationship between T4/T8 ratios and these functions has not been explored.

We investigated neutrophil function and T4/T8 ratios simultaneously in 38 patients (mean burn size 38·7 per cent). Immunological assays were performed twice weekly and cultures were taken from wound, blood, urine, sputum, intravascular lines and other clinically indicated sites.

	Chemotactic index	*P	Bactericidal capacity	*P	T4/T8
Sepsis (*n*=25)	0·51±0·26	<0·2	60±34%	<0·05	2·4±1·1
No sepsis (*n*=13)	0·64±0·21		75±27%		2·7±1·7
Survivors (*n*=28)	0·6±0·22	<0·2	69±31%	<0·05	2·4±1·1
Non survivors (*n*=10)	0·45±0·2		50±30%		2·5±1·4

* Unpaired Student's t test

Following thermal injury serial assays of neutrophil chemotaxis and bactericidal function can be used to anticipate the development of septic complications and the clinical outcome. There is no correlation between T4/T8 ratios and neutrophil function or prognosis.

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Retinal microembolism during cardiopulmonary bypass

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To elucidate the pathophysiological basis of diffuse cerebral injury found in many patients after cardiopulmonary bypass, 36 patients undergoing cardiac surgery were studied with retinal fluorescein angiography to assess the incidence of microembolism in the territory of the internal carotid artery. All (23/23, 100 per cent) of patients studied on the operating table during cardiopulmonary bypass had retinal microvascular occlusions consistent with microembolism, irrespective of whether or not an arterial line filter was incorporated in the bypass circuit. Of these (4/5, 80 per cent) patients restudied 30 min after discontinuation of bypass had persistent occlusions, and 2/29 (6·9 per cent) patients restudied at a median of 8 days postoperatively had occlusions. Three control non-bypass patients had normal retinal perfusion during cardiovascular surgery.

0007–1323/87/060526–23$3.00

In a parallel study of 20 dogs, 10/11 (90·9 per cent) dogs undergoing bypass without arterial line filtration had retinal microvascular occlusions, but only 4/9 (44·4 per cent) dogs had occlusions when a 40 μm polyester screen arterial line filter was used. In the unfiltered group 7/11 (63·6 per cent) dogs had platelet-fibrin plugs in the retinal microcirculation on histology. Six dogs undergoing sham bypass had normal retinal perfusion.

In conclusion, we have demonstrated for the first time *in vivo* that microvascular occlusions frequently occur in the cerebrovascular microcirculation during cardiopulmonary bypass.

Dynamic hepatic scintigraphy for the prediction of recurrent variceal bleeding

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Recurrent bleeding in patients with oesophageal varices has a high mortality in spite of initial control in approximately 90 per cent of cases[1]. The identification of patients at risk of further haemorrhage, however, remains difficult.

We have assessed the role of dynamic hepatic scintigraphy using ^{99m}Tc sulphur colloid to measure the mesenteric fraction (MF) and degree of portosystemic shunting[2] in 56 patients with compromised portal venous circulations (46 with cirrhosis, 10 with extrahepatic portal occlusion, EHPO). The results were compared with a group of 33 controls. Patients were followed for a median period of 24 months and the development of rebleeding correlated with the initial MF.

	Cirrhosis	EHPO	Control
Initial mean MF	$0{\cdot}30 \pm 0{\cdot}17$	$0{\cdot}27 \pm 0{\cdot}14$	$0{\cdot}58 \pm 0{\cdot}09$
Non-bleeders	$0{\cdot}39 \pm 0{\cdot}17$	$0{\cdot}40 \pm 0{\cdot}15$	
Rebleeders	$0{\cdot}20 \pm 0{\cdot}13$	$0{\cdot}15 \pm 0{\cdot}07$	
	$P < 0{\cdot}01$	$P < 0{\cdot}001$ (mean ± s.d.)	

These results demonstrate that patients with variceal bleeding and a low initial mesenteric fraction have a significant risk of re-bleeding despite active prophylactic treatment.

In conclusion, a group of patients at risk of recurrent bleeding can be recognized by non-invasive scintigraphy.

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Somatostatin analogue SMS 201 995: a solution to the dumping-diarrhoea syndrome after gastrectomy or vagotomy?

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The dumping-diarrhoea syndrome (DDS) which may follow partial gastrectomy or truncal vagotomy and drainage is often refractory to treatment. The aim of this study was to investigate a possible role for SMS in this condition.

Seven patients with a mean age of 54 years (range 28–75) were severe DDS after various types of gastric operation were studied. Dumping provocation tests (DPT) with 350 ml 25 per cent dextrose were carried out 30 min after subcutaneous injection of placebo, SMS 50 μg or SMS 100 μg, given in random order on separate days. Packed cell volume and blood glucose concentration were measured over the 2 h of the test.

With placebo, all patients experienced severe symptoms, often in combination: six had early dumping (ED), three late dumping (LD) and five had diarrhoea (D). After either dose of SMS symptoms of LD were abolished, and those of ED and D abolished in six patients and ameliorated in one case ($P < 0{\cdot}05$). The median increase in PCV in six ED patients was 5 per cent (range 2·5–8) on placebo, 0·5 per cent (range 0–5·5) after 50 μg SMS and 2 per cent (range 0–7·5) after SMS 100 μg ($P < 0{\cdot}05$). Blood glucose decreased by 2·8 (range 1·6–3·3) mmol/l in three LD patients but did not decrease after either dose of SMS.

SMS is an effective treatment of the DDS provoked by hypertonic glucose. 50 μg SMS is as effective as 100 μg. SMS may be a useful treatment for intractable DDS.

Collagenolytic activity in Crohn's colitis

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The aetiology of transmural inflammation, fissuring and fistula formation in Crohn's disease is unknown but may be due to a biochemical cause. Increased collagenase activity is associated with inflammation and tissue breakdown and may be the responsible agent. If so, such a biochemical abnormality should predate the macroscopic changes. Collagenase activity was therefore measured *in vitro*, by degradation of ^{14}C-labelled native mammalian collagen[1] in macroscopically normal colonic mucosa (mac-M) and seromuscular (mac-SM) layers of patients undergoing resection for Crohn's colitis ($n = 8$). Activity was also measured in macroscopically involved bowel from these patients and in histologically normal colon from 20 control patients.

	Collagenase activity (CPM h^{-1} mg^{-1} protein)		
	mac-M	mac-SM	Crohn's tissue
Controls	0·032*	0·0†	—
($n = 20$)	(0·0–3·67)	(0·0–1·15)	
Crohn's colitis	3·47*	2·01†	12·03
($n = 8$)	(0·11–4·54)	(0·01–5·69)	(3·62–48·60)

Values are medians ± range *$P < 0{\cdot}002$, †$P < 0{\cdot}002$, Mann–Whitney *U* test

Collagenase activity was detected in the mac-SM layer in all eight patients (100 per cent) with Crohn's colitis (compared with 2 (10 per cent) of controls, $\chi^2 = 6{\cdot}04$, $P = 0{\cdot}014$). Mac-M and mac-SM layers from Crohn's colitis patients contained significantly higher activity than control bowel ($P < 0{\cdot}002$) respectively). Highest activity occurred in macroscopically involved Crohn's tissue (compared with control bowel wall $P < 0{\cdot}002$). Increased collagenase activity is found in macroscopically normal bowel of patients with Crohn's disease and appears a precursor of macroscopic changes. Inhibition of this activity may thus prevent progress of the disease.

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Anastomotic arteriovenous fistulae—are they worth it?

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An adjuvant distal arteriovenous (A–V) fistula has been claimed[1,2] to increase arterial bypass graft flow and patency when run-off is poor; however others have suggested that a patent fistula sacrifices any improvement in distal limb perfusion[3].

Adjuvant distal A–V fistulae were constructed in ten grafted dog hind limbs, the ten contralateral limbs being grafted as controls. Flow and pressure within each graft and distal artery was measured during temporary occlusion and release of the venous limbs of the fistula. These measurements were repeated at re-operation 3 months later.

Mean flow through control grafts was 83 ± 27·1 ml/min, increasing to 146 ± 72·4 ml/min with papaverine ($P < 0{\cdot}001$), and was unchanged at 3 months. Mean flow in grafts with a distal A–V fistula was 250 ± 131·8 ml/min with no change after papaverine, and an increase to 730 ± 349·3 ml/min at 3 months ($P < 0{\cdot}001$). However, arterial flow distal to the fistula was invariably retrograde at initial operation (20 ± 9·5 ml/min), and this retrograde flow increased to 180 ± 105 ml/min at 3 months ($P < 0{\cdot}001$). Distal arterial pressure at initial operation fell from 88·8 ± 10·6 mmHg to 10·8 ± 3·2 mmHg with the fistula open.

We conclude that whilst an adjuvant distal arteriovenous fistula may improve bypass graft flow, it is unlikely to benefit distal limb perfusion.

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Transvascular protein exchange in the ischaemic limb

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Post-ischaemic limb swelling following re-vascularization may be related to microvascular changes associated with ischaemia[1]. We determined transvascular protein movement by lymph-to-plasma ratio (*L/P*) and lymph flow (Q_L) in a passively flexed intact dog hind limb during 1 h of steady state (C), 6 h of aorto-iliac occlusion (I), and 3 h of reperfusion (R). Central pressures, femoral arterial (P_A) and venous pressures and Q_L were recorded every 15 min. Animal groups included: GI, sham operation ($n=5$); GII, moderate ischaemia (P_A=30–45 per cent C, $n=7$); and GIII, severe ischaemia (P_A=5–20 per cent C, $n=7$). Lymph flow increased over 10 h in control animals without change in *L/P*. In GII, Q_L decreased during I and remained low during R without a change in *L/P*. Severe ischaemia caused an increase in *L/P* despite a fall in Q_L and *L/P* remained elevated during R as Q_L exceeded baseline.

	Group	Steady state (C)	Ischaemia (I)	Reperfusion (R)
L/P	GII	0·42±0·1	0·38±0·12	0·36±0·11
	GIII	0·42±0·08	0·64±0·23*	0·63±0·18*
Q_L (mg/h)	GII	3·55±2·02	0·92±0·53**	1·95±1·86*
	GIII	1·91±2·06	0·14±0·11*	2·56±2·14

*$P<0{\cdot}001$, **$P<0{\cdot}0001$; analysis of variance repeated measures model All values are mean ±s.d.

A significant increase in wet to dry weight ratio of ischaemic to non-ischaemic muscle after reperfusion was noted only in GIII, 3·82±1·17 *versus* 2·60±0·45 ($P<0{\cdot}04$ paired *t* test). We conclude that severe ischaemia produces microvascular changes which increase transvascular protein flow, and leads to muscle swelling during reperfusion.

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The influence of distension pressure on medial integrity in human saphenous vein arterial bypass grafts

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Incidental medial and intimal damage caused during surgical preparation of venous artery bypass grafts can predispose to subsequent luminal thrombosis or to later atherogenesis. We studied medial functional integrity by measurement of ATP concentration and ATP/ADP concentration ratio.

Surgical preparation involving dissection, side-branch ligation, partial adventitial stripping, distension at less than 300 mmHg in iso-osmotic NaCl solution at 23°C caused a fall in ATP concentration from 270±20 nmol/g wet weight ($n=25$) to 140±30 nmol/g ($n=12$, $P<0{\cdot}01$) and in ATP/ADP ratio from 2·3±0·1 to 1·2±0·2 ($P<0{\cdot}01$). Distension alone at 300 mmHg reduced ATP concentration to 130±20 nmol/g ($n=14$, $P<0{\cdot}01$) and ATP/ADP ratio to 1·7±0·1 ($P<0{\cdot}01$). De-endothelialized vein had an ATP concentration of 270±20 nmol/g ($n=9$, NS) and an ATP/ADP ratio of 2·3±0·2 (n.s.) showing the changes in surgically prepared or distended vein to reflect medial damage. Surgical manipulation alone, storage alone for 2 h in NaCl solution or distension at 150 mmHg did not reduce either ATP concentration or ATP/ADP ratio.

The data show that medial damage occurs during distension but only at pressures above 150 mmHg. It is therefore not an inevitable consequence of implantation into the arterial circulation. Surgical techniques which avoid luminal over-distension need to be used in order to implant functionally intact grafts.

A new method of determining calf vessel patency

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The decision to perform femorodistal bypass is usually based on the presence of adequate calf vessel run-off. Conventional arteriography and Doppler ultrasound may fail to detect patent vessels if the limb is severely ischaemic and give little haemodynamic information.

We have developed a non-invasive system based on a standard Doppler ultrasound velocimeter and a sphygmomanometer cuff driven by pulsatile compressed air. The cuff is placed around the upper calf and the pulsatile pressure generates blood flow in the calf vessel. Patent vessels can be detected by a Doppler probe at the ankle even if the existing signal is inaudible. Allen's test can also be easily performed to determine continuity with the pedal arch.

Pressure generated run-off (PGR) has been compared to arteriography in 95 ischaemic legs. Both were compared to the peripheral resistance at operation in 59 legs. Arteriography was inadequate in 17 cases (18 per cent) but PGR could be performed in all cases. There was a highly significant correlation between the PGR and arteriogram scores ($r=0{\cdot}95$).

The peripheral resistance correlated better with the PGR than the arteriogram score ($r=0{\cdot}94$ *versus* 0·85). PGR was also better than arteriography at predicting a successful graft outcome (sensitivity 97 per cent *versus* 72 per cent and specificity 61 per cent *versus* 55 per cent).

PGR is a quick, easy, non-invasive method of assessing calf vessel patency prior to femorodistal bypass. It is inexpensive as it can be used with any existing Doppler and usefully supplements pre-operative arteriography.

Thyroid dysfunction in women with peripheral arterial disease

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Established risk factors for peripheral arterial disease include smoking and diabetes. Autoimmune thyroiditis is common in elderly women (7 per cent) and considered as a risk factor for coronary heart disease. The prevalence of thyroid dysfunction in women attending an arterial clinic for claudication or rest pain was investigated using a sensitive immunoradiometric assay for thyrotropin (TSH).

The normal range of TSH in elderly women was established in controls ($n=30$) with a normal exercise test[1]. Among 80 consecutive patients, 7 were already taking thyroxine for myxoedema. A further 15 patients had an elevated serum TSH of whom 9 had positive thyroid antibodies and 3 had a low serum T4.

	Mean age	Mean TSH (milli-units/l)	Median TSH (milli-units/l)	Raised TSH	Smokers	Cholesterol (mmol/l)
Controls	68±7·2	1·6±1·1	1·5	1	17%	6·3±1·0
Patients	70·5±8·8	3·7*	2·4*	15	59%	7·0±1·3**

Results expressed as mean ±s.d.; *significantly different from controls; $P<0{\cdot}001$ or **$P<0{\cdot}1$

The overall incidence of thyroid dysfunction amongst the patients was 27·5 per cent compared to only 3·3 per cent in the controls. This demonstrates a definite association between thyroid dysfunction and arterial disease in women. Any possible benefits of treating arterial disease in patients with borderline hypothyroidism could best be assessed in a multicentre, double-blind trial.

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What compression heals chronic venous ulcers?

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Compression of 35–40 mmHg is thought to prevent capillary transudation in legs with venous disease[1]. To achieve this, four-layer compression bandaging (4LB) consisting of Velband (Johnson and Johnson), crepe, Elset (Seton Products), and finally cohesive elastic Coban (3M Health Care) was evaluated.

Pressures at the ankle and three points on the calf under the 4LB were compared to those under Elastoplast bandaging in 20 individuals using a Medical Stocking Tester (Salzman Limited). The 4LB was then applied to 148 legs with chronic venous ulcers which had failed to heal for a mean of 27·2 ± 8 months despite previous Elastoplast bandaging.

	Pressure (mmHg)			
	Medial malleolus	Gaiter	Mid-calf	Below knee
Elastoplast	22·5 ± 1·8	19·4 ± 1·9	12·9 ± 2	5·8 ± 0·5
Four-layer	42·5 ± 1*	38·8 ± 1·5*	35·1 ± 1·3*	17·2 ± 1·7*

Values are mean ± s.e.m.
*$P < 0·001$ compared with Elastoplast

The 4LB achieved significantly higher pressures in all areas reaching 42·5 ± 1 mmHg at the ankle. In the ulcer patients, the mean age was 71 ± 1·7 years and area of ulcer 15·35 ± 6·8 cm^2 despite Elastoplast bandaging. Ulcer healing rate achieved 3·5 ± 1·2 cm^2/week in the second week following the start of 4LB. Of the 148 ulcers, 110 (74 per cent) healed completely within 3 months with a mean time to healing of 6·3 ± 0·4 weeks.

Compression of over 40 mmHg achieved rapid healing in chronic ulcers that had failed to heal in many months of bandaging with lower pressures. This level of compression in clearly required for effective treatment.

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Surgery to the communicating veins in patients with healed venous ulcers does not improve calf pump function

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Graduated elastic compression stockings and surgical ablation of incompetent communicating veins with eradication of superficial varicosities are thought to prevent the recurrence of venous ulcers by reducing pressure in the superficial veins[1,2].

Volumetric foot plethysmography on exercise has been shown to correlate with foot vein pressure measurements[3], which are the best method of assessing calf pump function. Foot volumetry was performed on 35 limbs, with and without tourniquet, after healing of a venous ulcer, and repeated 12 months after treatment with either surgery or elastic compression stockings. Post-thrombotic changes were present on phlebography in 40 per cent of limbs. We have estimated the half volume refilling time ($TV_{1/2}$)—an assessment of reflux, and expelled volume (EV_{rel})—an assessment of calf pump function. $TV_{1/2}$ is the time in seconds required for half of the expelled volume to return to the foot following exercise. EV_{rel} is the reduction in foot volume during exercise divided by the volume of the foot (ml/100 ml).

Seventeen limbs were treated surgically and eighteen limbs were treated with elastic stockings. The initial foot volumetry measurements were significantly lower than normal. There was no improvement in $TV_{1/2}$ values 12 months after either form of treatment. There was a small but significant improvement in EV_{rel} after treatment with surgery and stockings.

We conclude that calf muscle pump function does not return to normal 1 year after either form of treatment. There is a small improvement in EV_{rel} in limbs treated with surgery and elastic stockings. We suggest that patients receiving either form of treatment should wear elastic stockings indefinitely.

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Relationship between tumour size and 17β-hydroxysteroid dehydrogenase activity in breast adipose tissue

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Steroid metabolism in breast adipose tissue may influence the local endocrine environment within the breast. The activity of 17β-hydroxysteroid dehydrogenase, a pivotal enzyme in the interconversion of both androgens and oestrogens, was measured in adipose tissue adjacent to 38 breast carcinomas. Particulate fractions were incubated with $(1\beta^3H)\Delta_4$ androstenedione and the radioactivity measured in purified characterized testosterone fractions.

Activity was detected in all tissue samples with a wide range of values: 0·03–53 pmol testosterone mg protein^{-1} h^{-1} (units). Levels were not related to the age, menopausal status, weight, obesity (Quetelet index: weight/height^2) or parity of the patients. Values, however, were significantly higher in the vicinity of tumours greater than 3 cm diameter at presentation ($n = 24$ median 2·45 (0·29–53 units) compared with smaller tumours ($n = 14$ median 0·89 (0·03–1·9 units, $P < 0·0001$, Wilcoxon rank test). This association was specific in that there was no correlation between tumour size and another steroid metabolizing enzyme (i.e. aromatase)[1].

These results, therefore, provide further evidence of the intimate interaction between breast adipose tissue and breast cancer.

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Altered catecholamine levels in women with benign breast disease

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Increased tissue cyclic AMP concentrations and enhanced adenylate cyclase responses to catecholamines have been reported in breast biopsies obtained from women with fibrocystic disease[1]. Raised urinary catecholamine levels are also described in such patients. Methylxanthines (MX) increase blood concentration of catecholamines; reduced intake is associated with resolution of symptoms in women with painful, nodular breasts[2].

We have compared the concentration of catecholamines and MX (caffeine, theophylline and theobromine) in the blood of 30 women with severe cyclical mastalgia with 17 healthy age-matched controls. During the luteal phase of the menstrual cycle, venous sampling was performed between 7 and 9 a.m., following overnight fasting and a standardized rest period.

MX levels were similar in both groups, but significant differences in adrenaline, noradrenaline and dopamine levels were observed between patients and controls (*see Table 1*).

Table 1 *Blood levels of catecholamines in mastalgia patients and controls*

	Adrenaline (pg/ml)	Noradrenaline (pg/ml)	Dopamine (pg/ml)
Mastalgia ($n = 30$)	1121 ± 228*	512 ± 50†	589 ± 66*
Controls ($n = 17$)	276 ± 57	403 ± 63	1250 ± 324

Values are mean ± s.d.; * $P < 0·001$; † $P < 0·02$ (Student's *t* test)

The results indicate that MX-mediated catecholamine release may be enhanced in women with breast pain, although measured differences could reflect the activity of other catecholamine-releasing agents. Low dopamine levels correlate with previous reports of altered prolactin dynamics in women with cyclical mastalgia.

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Increased expression of apocrine antigen in malignant breast disease

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It is generally accepted by oncologists that malignant potential within a breast is present throughout the organ. This has been termed 'field change'. It has been suggested that two monoclonal antibodies (McAb) 323/A3 and Cal[1,2] detect antigens that demonstrate this 'field change' in the breast biopsies of patients 'at risk' of developing breast carcinoma.

We have studied 27 patients with malignant breast disease who have had a benign breast biopsy at least one year earlier. Eighteen patients had ducto-lobular tissue present in both biopsies and nine had apocrine metaplasia in both biopsies. In seven out of nine patients who had apocrine tissue in both biopsies, 323/A3 McAb staining increased in the later malignant group. This change was statistically significant (χ^2 test, $P = 0{\cdot}034$). No significant change in staining was detected for 323/A3 in biopsies with ductolobular tissue or with Cal in either apocrine or ductolobular tissue.

The 323/A3 McAb identified an antigen in apocrine tissue which increased during the evolution of malignancy. Increasing expression of this antigen may herald impending malignant changes and thus prove to be a useful predictor of breast cancer risk.

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Effects of danazol on progesterone and oestrogen receptor incidence in benign breast disease

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Patients with benign breast disease may obtain a clinical response lasting for 6 months or more following treatment with Danazol[1], despite all hormonal parameters returning to pretreatment levels within 4 weeks[2]. This study was designed to investigate the action of Danazol on breast steroid hormone receptors and to determine whether observed changes could explain the prolonged clinical response.

Twenty-two patients with mastalgia and one with severe localized nodularity were treated with 100 mg Danazol b.d. for 6 months. Breast biopsies were performed under local anaesthesia before treatment and at 6 and 12 months, using a specially-designed instrument based on the Tru-cut principle. Specimens were immediately stored in liquid nitrogen and the receptor concentration assayed by the single saturation dose method[3]. Levels greater than or equal to 5 fmol/mg protein were regarded as positive.

	Incidence of receptor positive biopsies		
	Pretreatment	6 months	12 months
Progesterone receptor	9/23 (39%)	15/22 (68%)	18/23 (78%)
Oestrogen receptor	5/23 (22%)	10/22 (45%)	4/23 (17%)

There was a significant increase in progesterone receptor positive biopsies, $P<0{\cdot}05$ using McNemar's test. These data suggest that Danazol may induce progesterone receptors in the breast and that these changes may persist 6 months after cessation of treatment.

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The clonogenic growth of human breast carcinomas

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The clonogenic growth *in vitro* of single human cancer cells has been promoted in the USA as a valid means for *in vitro* chemosensitivity testing. Using the stem cell assay technique of Hamburger[1] we have studied the feasibility of cloning primary breast cancers and related growth to known biological prognostic variables and overall prognosis.

Of 71 primary tumours only 68 produced enough viable cells for assaying and in only 29 were there enough for testing one drug. In 15 direct comparisons, enzymatic disaggregation was superior to mechanical methods.

Of 68 tumours cultured only 24 grew tumour colonies. Growth was unrelated to age, menopausal status, histological type or grade. Oestrogen ($\chi^2 = 5{\cdot}69$, $P<0{\cdot}02$) and progesterone receptor negative tumours ($\chi^2 = 4{\cdot}13$, $P<0{\cdot}05$) grew preferentially. Growth was also improved in tumours with higher thymidine labelling indices (−TLI 'growers' with median TLI 0·65, range 0·1–7·1, 'non-growers' with median TLI 0·25, range 0·1–2·6) Mann–Whitney *U* test $P = 0{\cdot}048$. As most receptor negative tumours had higher TLIs it seems likely that growth medium supports receptor negative or biologically less differentiated tumours. No relationship with recurrence free survival and clonogenicity was noted following a median 5-year follow-up.

In conclusion, clonogenic growth is possible in this assay but is selective and yet refined enough for chemosensitivity testing in breast cancer.

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Epidermal growth factor receptor status of human breast cancers is related to early recurrence and death

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Epidermal growth factor receptors (EGFr) are detectable on some human breast cancers[1]. Studies of EGFr in bladder[2] and stomach[3] cancers suggest their presence is related to poor patient prognosis. EGFr was measured on 135 operable breast cancers by radio-ligand binding. Bloom and Richardson score, size of tumour, oestrogen receptor status (ER) and presence of node involvement were documented. We compared these with the relapse free survival (RFS) and overall survival (OS). Analysis was by χ^2 test, Peto log rank analysis and multiple-hazard ratios using Cox models.

The RFS and OS were worse for patients with EGFr positive tumours ($P<0{\cdot}001$ for both comparisons). RFS and OS were also worse for patients with ER negative tumours ($P<0{\cdot}025$ for both).

EGFr status divided ER negative patients into two groups. The RFS and OS for ER negative EGFr positive patients was worse than for ER negative EGFr negative ($P<0{\cdot}025$ for both). The RFS and OS for ER negative EGFr negative patients did not significantly differ from ER positive patients.

Cox model analysis showed EGFr status to be the most important variable in the primary tumours for predicting RFS and OS, the most important prognostic factor in node negative patients and second most important in patients with involved lymph nodes.

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Ultrasound localization for aspiration cytology of breast lumps

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Aspiration cytology has a high diagnostic accuracy after a satisfactory aspirate but the high rate of unsatisfactory aspirates leads to problems for both clinician and patient.

We have assessed whether ultrasound localization of the aspiration needle will improve the diagnostic accuracy. Ninety-six patients with palpable solid breast lumps were randomly allocated either to standard aspiration cytology ($n=50$) or to ultrasound localization cytology ($n=46$).

	Aspiration cytology alone ($n=50$)	Aspiration cytology with ultrasound ($n=46$)
Malignant	11	19
Benign	17	16
Equivocal	1	1
Satisfactory aspirate	29	36
Unsatisfactory aspirate	21 (42%)	10 (22%)**

**$P<0{\cdot}02$

The statistically significant reduction of unsatisfactory aspirates with ultrasound localization was mainly for tumours less than 3 cm diameter (unsatisfactory rate with aspiration cytology alone 49 per cent—with ultrasound 22 per cent $P<0{\cdot}04$).

Experience and technique are the most important factors in obtaining a satisfactory aspirate, but consideration should be given to ultrasound guidance for tumours less than 3 cm diameter to reduce the unsatisfactory aspirate rate.

The comparison of transmission spectroscopy (Lite-Scan) with mammography in the diagnosis of breast lesions

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Transmission spectroscopy has been developed as an aid to diagnosis in breast disease. This technique employs a combination of transillumination light scanning and spectroscopy using selected safe electromagnetic wavelengths in the visible and near-infrared range.

We have compared diagnostic accuracy of Lite-Scan with that of mammography in 164 patients referred to the breast clinic.

	Final diagnosis			Final diagnosis	
Mammography	Benign	Malignant	Lite-Scan	Benign	Malignant
Malignant/ indeterminate	29	25	Malignant/ indeterminate	44	26
Benign/normal	105	5	Benign/Normal	90	4
	Sensitivity 83·3%			Sensitivity 86·6%	
	Specificity 78·4%			Specificity 67·2%	

In the diagnosis of breast cancer transmission spectroscopy has a similar sensitivity to mammography but it is less specific. The techniques are complementary, with no cancer being diagnosed as benign disease when both investigations are combined.

Effects of verapamil and hypovolaemia on canine renal haemodynamics

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Verapamil reduces myocardial damage in haemorrhagic shock and protects post-ischaemic renal function in dogs. The effects of verapamil and hypovalaemia on renal haemodynamics were studied. Seventeen anaesthetized mongrel dogs were divided into three groups; A, not shocked, and given verapamil (2·28 µg/kg over 90 min); B, shocked (mean BP=40 mmHg for 2 h) and given saline; C, shocked and re-infusion of shed blood (III), and one hour after shock (IV). Total renal were monitored before shock (Period I), end of shock (II), after reinfusion of shed blood (III), and one hour after shock (IV). Total renal blood flow was estimated by 15 µm radio-labelled microspheres during each period (*Table*). Creatinine and osmolar clearance were estimated before and after shock.

		Renal blood flow (ml min^{-1} 100 g^{-1})			
	n	I	II	III	IV
A: Verapamil	5	834 (117)	417 (59)**	382 (46)	561 (52)*
B: shock + saline	5	637 (51)	37 (10)	382 (68)	377 (90)
C: shock + Verapamil	7	622 (41)	74 (11)	183 (39)*	320 (3)

Values are mean ± s.e.m.

*$P<0{\cdot}05$, **$P<0{\cdot}01$, ANOVA and Student's *t* test

Total renal blood flow fell during shock, failed to return to normal after re-infusion ('no reflow') and this was exacerbated in animals given verapamil. Despite this, no measureable difference in renal function was recorded between groups B and C. Calcium blockade had a deleterious effect on renal haemodynamics, thus limiting its use in haemorrhagic shock.

Isoflurane does not protect against focal cerebral ischaemia in primates

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Isoflurane is a volatile anaesthetic that is being used with increasing frequency for neurosurgical procedures. It reduces cerebral metabolism and electrocortical activity in a manner similar to the barbiturates. Recent reports suggesting that isoflurane is protective during global ischaemia have prompted the use of isoflurane clinically for cerebral protection despite evaluation in the more clinically relevant model of focal cerebral ischaemia.

Six hour middle cerebral artery occlusion was studied in 19 baboons. One group received thiopental titrated to produce deep EEG burst suppression. A second group received isoflurane adjusted to produce a similar EEG pattern. A control group received nitrous/narcotic anaesthesia. Because isoflurane produced hypotension, which is known to worsen infarction in this model, vasopressors were used in the isoflurane group, and vasodilators in the barbiturate group, in an effort to maintain mean arterial pressures within the range of 80–100 mmHg. Neurological and neuropathological outcomes were compared.

In the isoflurane group six of seven animals were hemiplegic. Three were obtunded and two died. All seven had pathologically verified infarcts. In contrast, only two of six thiopental animals suffered infarction. The nitrous/narcotic group had an intermediate outcome. Differences in the infarction rate and neurologic outcome between the isoflurane and thiopental groups were significant at $P<0{\cdot}05$ and $P<0{\cdot}055$ respectively. The present results suggest that isoflurane is not protective against focal ischaemia and should not be used when cerebral protection is required.

Tumour energy metabolism as a target for selective antineoplastic therapy

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Previous attempts to use tumour energy metabolism as a target for anti-neoplastic therapy have used single agents aimed at inhibiting either glycolysis or oxidative phosphorylation. Since most tumour cells use both pathways for energy production this approach is unlikely to succeed. The aim of this study was to manipulate simultaneously both sources of intracellular ATP to achieve more selective control of tumour growth.

Rhodamine 6G (R6G) is a fluorochrome mitochondrial dye which inhibits oxidative phosphorylation. 3-Mercaptopicolonic acid (3MPA) inhibits gluconeogenesis and is a potent hypoglycaemic agent in the fasting state. Groups of rats ($n=7$ per group) underwent subcutaneous implantation of Walker 256 carcinosarcoma. Following a 24 h fast each group received either saline, R6G (0·8 mg/kg), 3MPA (40 mg/kg) or the combination given intraperitoneally. Seven days after tumour implantation animals were sacrificed and tumours excised and weighed.

Administration of R6G during a period of hypoglycaemic significantly reduced the tumour growth rate when compared to control experiments (3·6±0·3 g *versus* 7·1±0·7 g, mean±s.e.m., $P<0{\cdot}05$). In contrast, neither R6G nor the period of hypoglycaemia alone significantly affected tumour growth.

These results suggest that simultaneous manipulation of oxidative phosphorylation and glycolysis may be used to selectively inhibit tumour growth *in vivo*.

The effect of different total parenteral nutrition regimens on hepatic triglyceride secretion

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Fatty infiltration is one of the earliest hepatic complications of total parenteral nutrition (TPN). In parenterally fed rats this is largely due to decreased hepatic triglyceride secretion[1]. Hepatic triglyceride secretion may be calculated in man from radiolabelled triglyceride turnover following intravenous ^{3}H-glycerol.

Twelve postoperative patients received TPN with 2000 dextrose calories (CHO-TPN). Fourteen received an identical regimen with 500 calories replaced by lipid emulsion (Lipid-TPN). Six patients received equal volumes of 4 per cent dextrose/0·18 per cent NaCl (D/S). On the seventh postoperative day triglyceride turnover was measured.

Regimen	n	Total triglyceride turnover (mg kg^{-1} h^{-1})	0–24 h integral (d.p.m. 24 h^{-1})
D/S	5	16·3+4·0	16 602+2850
Lipid-TPN	10	10·7+2·3	10 578+1208
CHO-TPN	11	12·2+2·9	26 696+3484*

Figures are means±s.e.m.; * differ from Lipid-TPN and D/S, $P<0{\cdot}05$

The three groups were comparable for age, weight, septic score, plasma triglyceride and free fatty acid concentrations. Resolvable curves were obtained from twenty-six patients. Total triglyceride turnover was similar in each group. The 0–24 h integral was significantly greater after CHO-TPN than either Lipid-TPN or D/S. This suggests that a higher proportion of the secreted triglyceride is synthesized in CHO-TPN patients from non-lipid precursors than in those receiving Lipid-TPN or D/S. Neither TPN regimen appeared to impair the liver's ability to secrete triglyceride, regardless of its origin.

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Resuscitation of haemorrhagic shock; an adverse effect of SPPS on renal function

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Previous work from this department[1] showed worse renal function in a group of dogs resuscitated from haemorrhagic shock with stabilized plasma protein solution (SPPS) than in a group resuscitated with saline. This study was designed to elucidate whether this difference was due to the Na load or whether it was a side effect of SPPS.

Anaesthetized greyhound dogs were subjected to severe haemorrhagic shock (40 mmHg for 90 min) then randomly allocated to resuscitation with normal saline ($n=10$), 3·5 per cent Polygeline ($n=9$), 6 per cent Hetastarch ($n=6$) or SPPS ($n=6$). Resuscitation was continued back to baseline pulmonary artery wedge pressure (PAWP) and the infusion rate was then titrated to maintain that PAWP for 60 min.

Following resuscitation, urine output was significantly worse in the SPPS group than in any other group and significantly better in the Polygeline and Betastarch groups than the saline group (*Table 1*).

Table 1 *Mean* (±*s.e.m.*)

	Normal saline	Polygeline	Hetastarch	SPPS
Volume of fluid required for resuscitation (ml)	2877 (288)	1195 (71)	1140 (58)	960 (98)
Urine output following resuscitation (ml h^{-1})	24·8* (3·6)	61·0 (16·5)	58·0 (18·5)	2·2* (1·1)

* $P<0{\cdot}005$

EVLW following resuscitation (*see Table 2*) was significantly higher in the saline group but this was primarily due to a significant fall in EVLW in each of the colloid groups. There was no difference in gas exchange between the groups.

Table 2 *Mean* (±*s.e.m.*)

	Normal saline	Polygeline	Hetastarch	SPPS
Initial EVLW (ml)	270 (29)	266 (18)	289 (22)	242 (23)
Post-resuscitation EVLW (ml)	312 (32)	218 (21)	202 (15)	200 (20)
	n.s.	$P<0{\cdot}005$	$P<0{\cdot}005$	$P<0{\cdot}005$

These results in conjunction with earlier data, while showing no clinically relevant difference in pulmonary function, suggest that SPPS is having an adverse effect on renal function.

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Oxygen radicals and endotoxaemia in the jaundiced rat

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This study examines the role of oxygen radicals in the fatal effect of endotoxin in the jaundiced rat. Obstructive jaundice was induced in rats by ligation of the common bile duct. Serum bilirubin, urea and creatinine were measured in controls and jaundiced rats 10 days after ligation of the common bile duct,

There were four study groups: controls were given endotoxin only ($n=10$) and jaundiced rats were given endotoxin only (J+E) ($n=10$), endotoxin and oxygen radical scavengers (J+E+S) ($n=16$) or endotoxin and allopurinol (J+E+A) ($n=10$). Scavengers used were superoxide dismutase, dimethyl sulphoxide and catalase, these and endotoxin were given by intravenous injection. Allopurinol was given by gavage.

Serum creatinine was similar in controls (47·3±7·8 mmol/l) and jaundiced animals (40·3±16·3 mmol/l). Serum urea was higher ($P<0{\cdot}01$) in jaundiced rats (6·9±1·6 mmol/l) than controls (5·8±2·3 mmol/l). Serum bilirubin was similar in the 3 jaundiced groups, 158·1±32·5, 188·1±39·2, and 172·3±29·6 mmol/l. Following injection of endotoxin only all controls survived, all J+E died, all J+E+A died. In the J+E+S group, nine died and seven survived, a significant difference compared to J+E ($P<0{\cdot}05$, $\chi^2=3{\cdot}96$). Bilirubin levels were similar in survivors (188·1±12·7 mmol/l) and those that died (180·0±12·9 mmol/l).

The protective effect of oxygen radical scavengers suggests oxygen radicals mediate the fatal effect of endotoxin in the jaundiced rat.

Demonstration of an extra-renal mechanism in sustained post-deoxycorticosterone hypertension

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Following renal transplantation sustained hypertension, despite bilateral host nephrectomy, may be attributable directly to the graft (e.g. renal artery stenosis or chronic rejection); alternatively it may be due to extra-renal mechanisms. Using an animal model of hypertension we have investigated the possible role of extra-renal mechanisms in maintaining hypertension after successful renal transplantation and in the absence of graft rejection.

Hypertension was induced in male Lewis rats following unilateral nephrectomy by administering deoxycorticosterone (DOC) (12·5 mg thrice weekly) and 1 per cent NaCl + 0·2 per cent KCl as drinking water for 4 weeks. Systolic blood pressure was measured using an indirect technique. Renal transplantation, with removal of host kidney(s), was performed 10 weeks post-DOC and blood pressures recorded for 12 weeks after transplantation. Renal transplantation ($n=17$) between normotensive animals failed to alter recipient blood pressure. Normotensive animals ($n=8$) which received kidneys from hypertensive rats remained normotensive. Lastly, hypertensive rats ($n=8$) underwent renal transplantation from normotensive animals. Although this initially lowered blood pressure, (146 ± 5 mmHg 1 week post-transplant) there was a progressive rise in blood pressure subsequently and by 6 weeks the animals were markedly hypertensive (180 ± 13 mmHg, $P<0{\cdot}001$).

This study suggests that extrarenal mechanisms, such as peripheral vascular reactivity, can maintain hypertension despite the presence of normal renal function and provides one explanation for failure of bilateral host nephrectomy to improve blood pressure control.

The influence of aspirin on pulmonary physiology in major surgery

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Thromboxane release during major surgery may mediate depression of cardiac and pulmonary function[1]. The effect of cyclo-oxygenase inhibition on pulmonary physiology during aortic surgery has been studied in pigs.

Twenty-four pigs weighing between 20 and 25 kg were randomized to low dose (LD) aspirin (0·5 mg/kg), high dose (HD) aspirin (10 mg/kg) or placebo. Arterial and Swann–Ganz catheters were inserted prior to midline laparotomy, small bowel exteriorization, 1·5 h of aortic clamping and 1 h shock before resuscitation. On induction, during shock and at 3 days, platelet and leucocyte counts, venous aggregates by screen filtration (SFP), mean arterial pressure (BP), cardiac output (CO), pulmonary vascular resistance (PVR), pulmonary shunt (PS) and alveolar-arterial PO_2 difference (A–adO_2) were measured.

	During surgical shock				
	SFP	Fall in BP (mmHg)	Fall in CO (l/min)	PS (percentage of CO)	A–adO_2 (mmHg)
Placebo	1·94 ± 1·01	35·5 ± 9·7	0·88 ± 0·1	8·7 ± 2·8	21·9 ± 3·8
LD aspirin	1·28 ± 0·46	9·0 ± 7·1*	0·66 ± 0·1	4·9 ± 1·3	11·9 ± 3·7*
HD aspirin	1·15 ± 0·31	11·2 ± 6·9*	0·56 ± 0·15	4·0 ± 1·7*	7·7 ± 2·2*

Results as mean ± s.e.m. *$P<0{\cdot}05$; Mann–Whitney *U* test compared to placebo

During shock following aortic declamping the fall in blood pressure was significantly less with aspirin despite failing to preserve CO ($P<0{\cdot}05$). Both PS and A–adO_2 were reduced ($P<0{\cdot}05$). Aspirin had little effect on SFP of venous aggregates and platelet counts fell in all groups. The improvement in PS but not A–adO_2 was still seen at 3 days.

Aspirin improved pulmonary haemodynamics and function during surgical shock. This benefit was less apparent by the third postoperative day and appeared to be due to a direct effect of cyclo-oxygenase inhibition in pulmonary microvasculature.

1. Utsunomiya T, Jrausz MM, Dunham B *et al.* Maintenance of cardiodynamics with aspirin during abdominal aortic aneurysmectomy (AAA). *Ann Surg* 1981; **194**: 602–8.

The effect of smoking on the permeability of the arterial wall

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The association between atherosclerosis and cigarettes is well recognized since over 90 per cent of patients with intermittent claudication are smokers. The mechanism which results in cigarettes being such a potent risk factor is uncertain. We have therefore investigated the effect of smoking on permeability of the arterial wall.

A polystyrene capsule containing Ringer solution was placed around the superficial femoral arteries of anaesthetized, intubated, non-surviving greyhound dogs. ^{125}I-labelled fibrinogen was injected intravenously, and the rate at which it crossed the arterial wall into the Ringer solution measured.

Two groups of arteries were studied: a control group (ten arteries in six dogs) and a smoking group (eleven arteries in seven dogs). The dogs in the test group breathed spontaneously through a two-way 'Ambu' valve, which was adapted to accept a cigarette holder. Mean resting carboxyhaemoglobin levels of both groups was 1·59 per cent (s.e.m. ± 0·10), this rose to a mean of 7·6 per cent (s.e.m. ± 1·15) in the smoking group after smoking 4 cigarettes an hour for 2 h, at which point permeability measurements were started. The CoHb levels had risen to a mean of 12·88 per cent (s.e.m. ± 0·87) at the end of the experiment, which lasted 3 h.

Table *Mean permeability coefficient* ($cm^{-2} \times 10^{-4}$)

Time (min)	30	60	90	120	150	180
Controls (mean ± s.e.m.)	3·08 ± 0·23	6·72 ± 0·54	8·28 ± 0·63	9·43 ± 0·80	10·76 ± 0·78	11·94 ± 0·94
Smoking (mean ± s.e.m.)	3·89 ± 0·54	8·40 ± 0·67	10·92 ± 0·76	12·94 ± 0·96	13·86 ± 0·97	14·63 ± 1·19

$P<0{\cdot}001$, analysis of covariance

We conclude that, in this experimental model, smoking increases the permeability of the arterial wall to ^{125}I-labelled fibrinogen.

The surgical importance of the anal transitional zone in ulcerative colitis

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The anal transitional zone (ATZ) lies between anal skin and rectal epithelium, extends proximally from the dentate line for 6–20 mm and contains various types of epithelium. It is removed during mucosal proctectomy and pouch–anal anastomosis. However, the importance of this zone for anal sensation and continence has been shown[1,2] and its preservation could improve the functional results after operation.

Using light microscopy with alcian blue and haemotoxylin and eosin staining, we examined 4–6 serial longitudinal sections of 31 proctolectomy specimens of histologically proven ulcerative colitis (UC) and 20 control proctocolectomy specimens of rectal carcinoma. Average mean histological lengths of ATZ were 8·5 mm (range 4–23) in UC and 6·6 mm (range 4–14) in controls. Macroscopic alcian blue staining correctly identified the extent of ATZ in 92 per cent of UC and 83 per cent of control specimens. No histological evidence of UC was seen in the ATZ in 61 per cent of UC specimens and 39 per cent showed mild inflammatory changes only at the upper border.

Table *Epithelial variants in ATZ*

	UC	Controls
Transitional	90%	47%
Mature squamous	5%	41%
Immature squamous	0%	12%
Columnar islands	5%	0%

The ATZ in UC is a macroscopically identifiable area of significant length above the dentate line with mainly transitional mucosa which is largely uninvolved by UC and can safely be preserved. Mucosectomy could thus be 'rectal' rather than 'anal', leaving the entire anal canal intact.

1. Duthie HL, Gairns FW. Sensory nerve endings and sensation in the anal region. *Br J Surg* 1960; **47**: 585–8.

2. Duthie HL, Bennett RC. The relation of sensation in the anal canal to the functional anal sphincter: a possible factor in anal continence. *Gut.* 1963; **4**: 179–82.

The relationship of p62$^{\text{c-myc}}$ in operable breast cancer to patient survival and tumour prognostic factors

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The protein product of the m-myc oncogene (p62$^{\text{c-myc}}$) is nuclear-associated and can be measured, by flow cytometry, in suspensions of nuclei from paraffin embedded tumour tissue using the monoclonal antibody myc a-6E10[1].

The aims of this study were to confirm that p62$^{\text{c-myc}}$ could be quantitated in the nuclei of breast cancers and to correlate these levels with patient survival and tumour prognostic factors.

p62$^{\text{c-myc}}$ levels were measured in the paraffin-embedded primary tumour tissue of 68 consecutive pateints treated for operable breast cancer between 1974 and 1975 using monoclonal antibody myc a-6E10.

After 4 years follow-up ten patients with p62$^{\text{c-myc}}$ levels greater than 80 fluorescence units (FU) had a significantly worse survival (33 per cent) than those patients with oncoprotein levels less than 80 FU (71 per cent) ($P<0{\cdot}05$).

There were significant associations between higher levels of p62$^{\text{c-myc}}$ and poor histological grading ($P<0{\cdot}05$) and lymph node involvement ($P<0{\cdot}05$):

	Histological grade			Lymph node stage	
p62$^{\text{c-myc}}$	1	2	3	Negative	Positive
<50	7	11	25	24	19
>51	3	14	7	7	16
	$\chi^2=7.2$ (2 d.f.)			$\chi^2=3{\cdot}87$ (1 d.f.)	

There was no correlation between p62$^{\text{c-myc}}$ levels and DNA index

C-myc oncogene protein product is thought to be involved in the control of cell proliferation. High levels of p62$^{\text{c-myc}}$ in breast cancers are associated with poor prognostic parameters and a significantly worse survival.

1. Watson JV, Sikora K, Evans GI. A simultaneous flow cytometric assay for c-myc oncoprotein and DNA in nuclei from paraffin embedded material. *J Immunol Methods* 1985; **83**: 179–82.

Reduced axon reflex flare in diabetics with neuropathic foot lesions

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Peripheral nociceptive C fibres have the dual role of transmitting impulses responsible for pain centrally and for causing neurogenic vasodilatation peripherally to produce the axon reflex flare. Although loss of pain sensation is considered to contribute to the development of diabetic neuropathic foot complications, this relationship has not previously been quantitated. We have devised an objective method of measuring the flare as a measure of nociceptive C fibre function.

Forty-six controls, eleven long-standing diabetic patients (>10 years) with normal feet (Group 1), and sixteen diabetic patients with foot complications (Group 2) were studied. All had ankle/brachial Doppler indices greater than 1. The flare was stimulated by electrophoresis of 10 per cent acetylcholine for 5 min and non-neurogenic vasodilatation (Lewis's red reaction) was induced with a dermograph. Vasodilatation was measured with a laser Doppler flowmeter.

	n	Age (years)	Resting flux (mV)	Flare (mV)	Direct vaso-dilatation (mV)	
					n	
Controls	46	48·5±10·2	3·3±2·4	12·0±4·7	44	16·6±5·8
Group 1	11	46·3±12·6	3·9±3·3	12·7±6·4	6	16·5±6·3
Group 2	16	45·8±11·4	3·3±2·6	5·0±3·3*	14	14·4±4·5

Values are mean ± s.d.
*$P<0{\cdot}001$; Student's t test

In Group 1 there was no reduction in the flare response, while in Group 2 the flare was grossly reduced or absent although there was no significant reduction in the capacity of the vessels to dilate to direct stimulation. This indicates a severe impairment of nociceptive C fibre function in diabetic patients with foot complications, with the loss both of protective pain mechanisms and a component of the inflammatory response.

Rapid induction of major histocompatibility complex (MHC) antigens occurs in both rejecting and actively enhanced rat renal allografts

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Organ allografts undergoing unmodified rejection show a striking increase in donor MHC antigen expression which may increase their susceptibility to the rejection response[1]. The aim of this study was, using the DA into PVG rat renal allograft model, to compare the kinetics of MHC induction in rejecting and in non-rejecting actively enhanced allografts (pre-treatment with donor blood transfusion). Rejecting and enhanced kidneys were excised on days 1, 3, 5 and 7 ($n=5$ per group) and sections labelled with donor specific monoclonal antibodies MN4-91-6 (anti-class I) and F17-23-2 (anti-class II).

Both rejecting and enhanced allografts showed induction of class I antigens on tubular cells from day 1 onwards. Enhanced grafts unexpectedly showed *accelerated* induction of class II antigens with staining of tubules and arteriolar endothelium from day 3. These observations were confirmed by allospecific quantitative absorption analysis of homogenized pooled renal allografts. There was greater than a three-fold increase in class I and class II MHC antigens by day 3 in enhanced but not until day 5 in rejecting grafts.

Therefore, increased expression of MHC antigens within an allograft does not necessarily correlate with graft rejection and the suppressive mechanisms in active enhancement override rejection, despite increased target antigen density.

1. Milton AD, Spencer SC, Fabre JW. Detailed analysis and demonstration of differences in the kinetics of induction of class I and class II major histocompatibility complex antigens in rejecting cardiac and kidney allografts in the rat. *Transplantation* 1986; **41**: 499–507.

Cyclosporin and donor specific immunosuppression—an effective form of immunotherapy

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Donor-specific immunosuppression of graft rejection remains an important goal in transplantation. Although attainable experimentally, to achieve an optimum effect, it must be given one week or more before transplantation.

In this study, the effect of a low dose of cyclosporin with donor antigens was investigated in the rat in an attempt to reduce the time between pre-treatment and transplantation. In the LEW (RT1^{l}) to DA (RT1^{a}) strain combination, we have previously induced indefinite renal allograft survival (MST> 100 days) by pretreating recipients with 10^8 viable spleen lymphocytes seven days before transplantation[1]. Pretreatment with 10^8 cells one day before transplantation was ineffective (MST = 10 days). However 10^8 cells in combination with a 3-day course of 10 mg kg^{-1} day^{-1} of cyclosporin given on day −1, 0 and +1 resulted in the induction of prolonged allograft survival (MST> 100 days). Cyclosporin alone had no effect (MST = 10 days).

Thus it would appear that cyclosporin and donor-specific immunosuppression have an additive effect on prolonging renal allograft survival in the animal model. These findings suggest a possible mode of donor-specific immunosuppression that might be applicable to cadaveric transplantation.

1. Cranston D, Wood KJ, Morris PJ. Suppression of allograft rejection in the rat by normal but not heat inactivated or irradiated donor spleen cells. *Transplant Proc* 1985; **17**: 2421–2.

Monitoring the elective conversion from cyclosporin to azathioprine and prednisolone at 6 months post transplantation

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The elective conversion of renal allograft recipients from cyclosporin (CyA) to azathioprine and prednisolone has the advantage that the long-term risk of CyA nephrotoxicity, and also expense, is reduced. As conversion may precipitate a rejection episode we have monitored this period by fine needle aspiration cytology (FNAC) twice weekly for 4 weeks. Azathioprine (2 mg kg^{-1} day^{-1}) and prednisolone (15–20 mg day^{-1}) were introduced on conversion day 1 with reduction of CyA over the next 6–10 days.

As expected, the serum creatinine and alkaline phosphatase were significantly reduced and the mean creatinine clearance was significantly increased (*Table*). However FNAC exhibited increased mononuclear cellular infiltration in 13 of the 24 patients. In nine patients this was transient and there were no changes in the normal parameters of renal function. Four patients had rejection episodes with more pronounced FNAC changes which in three patients preceded the rise in serum creatinine. All four patients responded to methylprednisolone. However, two late rejection episodes (at 2 and 6 months) were steroid resistant and required reintroduction of CyA. No grafts were lost (with a follow-up period of 2–11 months).

This study has shown that although overt rejection occurred in 16·6 per cent of patients, cellular infiltration was present in over 50 per cent during conversion of immunosuppression.

	Pre-conversion	Postconversion
Serum creatinine	151 (119–176)	117 (100–147)**
Bilirubin	8·5 (7–10)	8 (5–10·5)
Alkaline phosphatase	11·8 (8·8–17·1)	10·6 (7·8–12·7)*
Creatinine clearance	56·5 (36–85).	85 (64–99)**

Values are median with interquartile range in parentheses; Wilcoxon signed rank test, *$P < 0{\cdot}05$, **$P < 0{\cdot}01$

Glycosylated haemoglobin levels in pancreatic islet cell transplanted rats

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Measurement on glycosylated haemoglobin (HbA$_1$) levels in the blood of diabetic patients is regularly used as a monitor of long-term glucose control. In this study we have measured the HbA$_1$ levels in islet cell transplanted rats with streptozotocin induced diabetes to determine whether HbA$_1$ levels give an accurate indication of glucose control.

HbA$_1$ levels were measured prior to and after induction of diabetes and post-transplantation with 750–1500 isologous pancreatic islets at 30, 60 and 120 days. Graft function was assessed by regular measurement of blood glucose and by use of the glucose tolerance test.

The mean HbA$_1$ level increased progressively after onset of diabetes (1·6 per cent, 3·2 per cent, 4·5 per cent, 6·7 per cent at weeks 0, 2, 4 and 6 respectively ($P < 0{\cdot}01$). All diabetic rats became normoglycaemic after transplantation and remained so throughout the study period. However, the mean glucose clearance (K) values were abnormal in the post-transplant animals (mean 1·3 per cent *versus* 2·3 per cent, $P < 0{\cdot}01$). The mean post-transplantation HbA$_1$ level was 2·8 per cent, 2·3 per cent and 2·1 per cent at 30, 60 and 120 days. Thus, the mean HbA$_1$ level was reduced by the transplant, but was still significantly higher than normal (1·6 per cent, $P < 0{\cdot}01$). Correlation between HbA$_1$ level and glucose clearance at 60 and 120 days were 0·951 and 0·92 respectively ($P < 0{\cdot}01$).

Thus, the HbA$_1$ level can be used as a sensitive indicator of glucose control in the islet cell transplanted rat.

Magnetic resonance imaging of renal transplants

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Differentiation of rejection from other causes of renal dysfunction, including cyclosporin nephrotoxicity, remains a problem in the management of the renal transplant patient. This preliminary study has examined the scope of magnetic resonance imaging (MRI) in the evaluation of the transplanted kidney.

Forty-four investigations were carried out in thirty-seven patients from 5 days to 4·5 years after renal transplantation. Using a 0·15 Tesla resistive imager, with a surface coil to improve the signal to noise ratio, a combination of the sequences, IR 100, IR 700 and SE 80 was found to provide maximal information in a time acceptable to the patient.

Eight patients, later proven to have acute rejection, were found to have complete loss of cortico-medullary differentiation and a characteristically altered vascular pattern, features not seen in grafts with normal function or cyclosporin nephrotoxicity. In addition, nine perinephric collections (six haematomas, three lymph collections), two obstructed collecting systems and one infarcted upper pole were demonstrated using the above sequences. Examples of these abnormalities and of normally functioning renal transplants will be shown.

MRI offers a non-invasive method of evaluating the progress of renal allografts and, in practice, may be able to differentiate acute rejection from cyclosporin nephrotoxicity.

Total corrected increment—an irrelevance in transplant aspiration cytology

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Rejection is the major problem following renal transplantation. Cyclosporin has improved graft survival but necessitates the distinction of rejection from drug nephrotoxity. Core biopsy is the best method of diagnosing the cause of allograft malfunction but is not repeatable daily because of its associated morbidity. Fine needle aspiration biopsy is repeatable but the fashion to correct for blood contamination by an arbitrary total corrected increment score[1], said by its proponents to be critical, makes it complex.

We assessed seventy-five aspirates by a cytospin technique and May–Grunwald–Giemsa staining in forty patients immunosuppressed with cyclosporin. The assessment was based on morphology and qualitative assessment of cellular infiltrates but *no* total corrected increment.

	Number of diagnoses	Number of correct FNAS	Number of incorrect FNAS	Sensitivity: specificity
Normal function	57	54	3	95%:100%
Rejection	10	10	0	100%:95%
Cyclosporin nephrotoxicity	8	7	1	88%:99%
Total		71		

Four incorrect diagnoses were made. All were early in the study. Fine needle aspiration like all other techniques was not good at detecting drug toxicity morphologically. It is unnecessary to calculate the arbitrary total corrected increment when an experienced renal histopathologist is available to assess cytology.

1. von Willebrand E. Fine needle aspiration cytology of human renal transplants. *Clin Immunol Immunopathol* 1980; **17**: 309–22.

Transplantation of isolated rat hepatocytes

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The successful transplantation of isolated hepatocytes into the spleen, although experimental, may offer a useful adjuvant in the treatment of acute and chronic liver disease. This study has examined the ability of rat hepatocytes, isolated by *in situ* collagenase perfusion[1], to colonize the spleen of syngeneic recipients and to survive after transplantation into allogeneic recipients.

Isolated Lewis hepatocytes (10^7) transplanted into the spleens of unmodified syngeneic recipients showed at day 30 ($n=6$) scattered nodules of surviving hepatocytes. Attempts to produce a hepatoproliferative stimulus by either CCl_4 induced cirrhosis ($n=12$) or secondary biliary cirrhosis ($n=6$) resulted in a striking proliferation of the transplanted hepatocytes with splenic colonization in all cases by day 30. Hepatocytes transplanted across a shared major but disparate minor histocompatibility barrier (F344 into Lewis) were rapidly rejected by day 3 ($n=6$) but administration of cyclosporin A ($15\ mg\ kg^{-1}\ day^{-1}$) prevented rejection ($n=6$). In contrast cyclosporin A failed to prevent the rapid rejection of hepatocytes transplanted across a major histocompatibility barrier (DA into PVG, $n=6$).

These results show that transplanted hepatocytes will, in the presence of a hepatoproliferative stimulus, produce splenic colonization. However, the clinical application of this technique may be limited by the apparent susceptibility of fully allogeneic hepatocytes to rapid rejection.

1. Seglen PO. Preparation of isolated rat liver cells. *Methods Cell Biol* 1976; **13**: 29–83.

The influence of anti-lymphocyte globulin (ALG) on late results of renal transplantation

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Between 1974 and 1985 we performed 264 transplants using prednisolone and azathioprine as initial immunosuppression. Since 1983 ALG has been used to treat those cases with acute rejection with poor prognostic histological features and early results were encouraging, particularly in males[1].

			Actuarial graft survival (%)					
		Number	3 month	1 year	2 year	3 year	5 year	7 year
Series prior to use of ALG	Male	105	65	62	56	53	48	34
	Female	59	68	62	52	50	48	32
Series with use of ALG	Male	49	90	83	63	59		
	Female	33	59	59	53	53		

The early beneficial effects of ALG in males has not been maintained. Of the 19 patients who received ALG and survived 3 months, 6 have subsequently lost their grafts and 3 more have advanced chronic rejection. In all 33 patients received ALG and only 10 now have stable graft function.

We conclude that the use of ALG to treat poor prognosis acute rejection only delays graft loss.

1. Cooksey G, Reeve RS, Nicoloupos N *et al.* Treatment of steroid resistant rejection of renal allografts with anti-lymphocyte globulin (ALG). *Br J Surg* 1985; **72**: 1024.

In vivo ^{31}P nuclear magnetic resonance spectroscopy of vascularized rat pancreatic transplants

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Fundamental changes in intracellular metabolism occur early in the acute rejection of vascularized organ transplants. The aims of this study are to ascertain whether or not ^{31}P nuclear magnetic resonance (NMR) spectra of segmental pancreatic grafts can be obtained *in vivo* and to evaluate the sensitivity of the method in detecting differences between rejecting and non-rejecting grafts in the rat.

DA–DA ($n=6$) and DA–Lewis ($n=6$) vascularized segmental pancreatic transplants were performed. Five days post-transplant, incisions were made, under general anaesthesia, adjacent to the grafts and NMR spectroscopy, using a surface coil tuned to the ^{31}P frequency, was carried out. Pre- and post-graft blood supply ligation spectra confirmed the absence of signal contamination from muscle.

Adenosine-triphosphate(ATP):inorganic phosphate(Pi) ratios and intracellular pH were calculated under uniform pulsing conditions for both isografts and allografts.

	ATP:Pi	pH
Isografts	1·43 ± 0·25	7·21 ± 0·04
Allografts	0·72 ± 0·2	7·01 ± 0·05

Values are mean ± s.e.m.

Both the ATP:Pi ratios and the pH were significantly lower for the allografts ($P=0{\cdot}03$ and $P=0{\cdot}008$ respectively, Mann–Whitney U test).

These studies suggest that ^{31}P NMR spectroscopy may be useful in assessing the physiological status of the transplanted pancreas and in defining the bioenergetics of early pancreatic rejection.

Aspiration cytology in the diagnosis of rejection after liver transplantation

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Fine needle aspiration cytology (AC) has proved of value in the diagnosis of renal rejection[1]. The aim of this study was to assess the value of AC in the diagnosis of hepatic rejection.

One hundred and seventy-four AC specimens from thirty patients undergoing thirty-six liver transplants were 'blindly' evaluated. Patients underwent protocol AC twice weekly and also when biochemical or clinical parameters suggested rejection. Hepatic rejection was only confirmed when clinical and biochemical changes were accompanied by positive histological diagnosis. Hepatic cellular constituents of lymphocytes, plasmablasts and plasma cells were compared with peripheral blood[1].

In 64 ACs demonstrating rejection, matched histology confirmed rejection in 57. In 39 ACs not suggesting rejection, matched histology showed no severe rejection, but features of mild rejection in 16. These figures give a sensitivity of 78·1 per cent and a specificity of 76·7 per cent. When, however, all AC samples were considered in which there were no biochemical or clinical features of hepatic rejection, then the sensitivity was 76·7 per cent specificity 86·9 per cent and positive predictive value 86·3 per cent.

Although histology remains the best standard in the diagnosis of acute rejection after hepatic grafting, AC may prove to be of value in monitoring liver transplant patients.

1. Hayry P, von Willebrand E, Ahonen J. Monitoring of organ allograft rejection by transplant aspiration cytology. *Ann Clin Research* 1981; **13**: 264–87.

A comparison of local and systemic effects of sepsis in determining survival

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Two separate scoring systems have been used to evaluate factors which determine survival in sepsis. The sepsis score (SS)[1] which takes into account local and systemic effects, and the APACHE II (APII)[2] score which relies almost entirely on the physiological effects of sepsis with a weighting for age and pre-existing disease. Sepsis was defined as evidence of thoraco-abdominal pus of more than 3 days duration. All scores were allotted on a weekly basis and the highest score used for analysis. Of 53 patients suitable for study, 8 were excluded because of incomplete documentation, 2 of whom died.

	Age	SS	APII
Survivors ($n=31$)	57 (19–90)	14 (10–26) *	12 (3–21) †
Non-survivors ($n=14$)	68 (22–86)	21·5 (11–32)	24 (15–38)

Values are medians and ranges, *$P<0{\cdot}05$, †$P<0{\cdot}01$, Mann–Whitney *U* test

Both the SS and APII were higher amongst non-survivors. The highest scoring 14 included 13 non-survivors in APII and 8 in the SS. Local factors constituted a mean of 54 per cent of the SS, and systemic effects 77 per cent of APII.

The greater accuracy of the APII in predicting survival would suggest that the systemic effects of sepsis are more important than the local disease in deciding outcome, and should comprise the main body of any scoring system.

1. Elebute EA, Stoner HB. The grading of sepsis. *Br J Surg* 1983; **70**: 29–31.
2. Knaus WA, Draper EA, Wagner DP *et al.* APACHE II: A severity of disease classification. *Crit Care Med* 1985; **13**: 818–19.

Effect of blood transfusion on host susceptibility to bacterial infection

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Blood transfusions improve renal graft survival and are associated with worsened prognosis following tumour surgery. Whether blood transfusion specifically affects the recipient's response to a bacterial challenge is unknown; however, high transfusion requirement incident to abdominal trauma is a significant risk factor for infection.

Male Lewis (LEW) rats were given 10 ml transfusions of syngeneic (LEW) or allogeneic (ACI) blood or a sham procedure. Immediately or 1 week post-transfusion, animals were challenged with a *Klebsiella pneumoniae* laden suture inserted into the thigh (TS) or caecal ligation and puncture (CLP). Blood bacterial counts were measured serially and mortality recorded 8 days after TS and 14 days after CLP. Log blood bacterial counts and mortality are shown in *Tables 1* and *2*.

Table 1 *Immediate thigh challenge*

	Sham	ACI	LEW
24 h	$2{\cdot}739 \pm 0{\cdot}266$	$3{\cdot}509 \pm 0{\cdot}278$	$3{\cdot}029 \pm 0{\cdot}255$
48 h	$2{\cdot}943 \pm 0{\cdot}178$	$3{\cdot}611 \pm 0{\cdot}250$*	$3{\cdot}429 \pm 0{\cdot}314$
72 h	$1{\cdot}050 \pm 0{\cdot}234$	$1{\cdot}456 \pm 0{\cdot}581$	$1{\cdot}748 \pm 0{\cdot}417$
Mortality at 8 days	0/16	5/13†	4/13†

Table 2 *1 week thigh challenge*

	Sham	ACI	LEW
24 h	$2{\cdot}015 \pm 0{\cdot}299$	$2{\cdot}841 \pm 0{\cdot}218$*	$2{\cdot}433 \pm 0{\cdot}185$
48 h	$2{\cdot}523 \pm 0{\cdot}182$	$2{\cdot}673 \pm 0{\cdot}170$	$2{\cdot}652 \pm 0{\cdot}182$
72 h	$0{\cdot}935 \pm 0{\cdot}256$	$0{\cdot}616 \pm 0{\cdot}212$	$0{\cdot}599 \pm 0{\cdot}184$
Mortality at 8 days	1/22	0/15	0/17

Values are mean ± s.e.m. *$P<0{\cdot}05$ non-paired *t* test *versus* sham; $P<0{\cdot}05$ Fisher's exact test *versus* sham

ACI rats had significantly higher bacteraemia 48 h after immediate TS and 24 h after late TS. Mortality was significantly higher in ACI and LEW groups after immediate TS, no difference was seen after late TS. No difference in bacteraemia or mortality was seen after immediate or late CLP. Mortality was higher after CLP than TS.

The result of severe bacterial challenge (CLP) was unaffected by transfusion, emphasizing degree of contamination as a major determinant of outcome. Transfusion adversely affected outcome after moderate challenge (TS), immediate challenge and allogeneic blood maximized this effect.

The effect of splenectomy on Gram-negative bacterial clearance in severe sepsis

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Severe sepsis leads to depression of the reticulo-endothelial system (RES) with delayed bloodstream clearance of particulate matter and bacteria[1,2]. Removal of the spleen (a major component of the RES) results in increased susceptibility to infection with encapsulated organisms[3] but its effect on the resistance to postoperative Gram-negative infection has been little studied.

We have investigated the effect of splenectomy on plasma fibronectin levels and bacterial clearance in the presence and absence of sepsis. In experiment 1, rabbits underwent splenectomy ($n=8$) or sham laparotomy ($n=6$) 4 weeks before a second laparotomy and measurement of RES function. In experiment 2, animals had either splenectomy ($n=8$) or sham laparotomy ($n=6$) followed 4 weeks later by devascularization of the appendix (sepsis). Plasma fibronectin levels and the blood clearance and organ distribution of an intravenous injection of ^{75}Se-labelled, viable *Escherichia coli* ($2–3 \times 10^8$ c.f.u.) were measured 24 h after the second operation.

Experiment	Fibronectin (percentage of control)	Blood clearance ($t_{\frac{1}{2}}$ (min))	Liver uptake (percentage ID/g)
1 Splenectomy	$84{\cdot}3 \pm 6{\cdot}5$*	$0{\cdot}72 \pm 0{\cdot}06$*	$0{\cdot}74 \pm 0{\cdot}04$*
Sham	$103{\cdot}0 \pm 6{\cdot}9$	$0{\cdot}46 \pm 0{\cdot}08$	$0{\cdot}09 \pm 0{\cdot}04$
2 Splenectomy + sepsis	$84{\cdot}0 \pm 7{\cdot}0$*	$1{\cdot}21 \pm 0{\cdot}11$*	$0{\cdot}57 \pm 0{\cdot}03$*
Sham + sepsis	$110{\cdot}8 \pm 3{\cdot}9$	$0{\cdot}88 \pm 0{\cdot}05$	$0{\cdot}73 \pm 0{\cdot}05$

Values are mean ± s.e.m. *$P<0{\cdot}05$ Mann–Whitney *U* test

Splenectomy resulted in a reduction in plasma fibronectin levels and delayed bacterial clearance with reduced liver uptake of *E. coli* which was even greater in severely septic animals.

In conclusion: (i) splenectomy results in depression of RES function with reduced plasma fibronectin levels and delayed *E. coli* clearance and (ii) in severe sepsis the impairment of RES function is more marked in the splenectomized animal. These results demonstrate the importance of the spleen and support the concept of splenic preservation.

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2. Chadwick SJD, Aldridge MC, Dudley HAF. Detection of reticuloendothelial blockade with low dose test agent. *Br J Exp Path* 1985; **66**: 483–91.
3. King H, Schumacker HB. Splenic studies I. Susceptibility to infection after splenectomy performed in infancy. *Ann Surg* 1952; **136**: 239–42.

The effects of thermal injury and immunoglobulin replacement therapy on IgG kinetics and IgG subset levels

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Trauma including severe burns induces immunological alterations which result in life-threatening infection[1]. IgG metabolism is severely deranged and diminished IgG levels can be prognostically related to a fatal outcome[2]. We investigated the effects of thermal injury and replacement therapy (IgG 500 mg kg^{-1} week^{-1}) on IgG kinetics and IgG subset levels in 20 patients (mean burn size 40·4 per cent) in a prospective controlled double blind study.

Circulating IgG levels and IgG_1 and IgG_3 subsets were diminished for 10 days following injury while IgG_2 and IgG_4 remained in the low normal range. Replacement therapy restored IgG, IgG_1 and IgG_3 values to normal and treated patients had significantly higher IgG_1, IgG_2, IgG_3 levels ($P<0{\cdot}05$). Following each infusion IgG levels fell rapidly over the first 24 h ($t_{\frac{1}{2}}=3{\cdot}8\pm1{\cdot}2$ days) and more gradually over the subsequent 3 days ($t_{\frac{1}{2}}=10{\cdot}8\pm3{\cdot}8$ days). The variation of early and late exponential decay constants with pre-infusion and peak IgG levels, burn size and 'post-burn' day was assessed by multiple linear regression analysis. The early rate of decline was influenced by proximity to the time of injury and pre-infusion value while later decline was related to peak levels and time of injury. Burn size did not influence the outcome.

Using this information IgG prophylactic and therapeutic regimens can be accurately determined, following thermal injury.

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2. Munster AM, Hoagland HC, Prutt BA Jr. The effect of thermal injury on serum immunoglobulins. *Ann Surg* 1970; **172**: 965–9.

Total parenteral nutrition does not improve anti-tumour lymphocytotoxicity in patients with gastrointestinal cancer

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Patients with malignant disease exhibit impaired immune responses which correlate with stage and prognosis. This may be a manifestation of impaired nutrition and it might be expected that nutritional supplementation would improve anti-tumour immune responses in these patients. To test this hypothesis anti-tumour and non-specific immunological function were measured before and after 7 days of total parenteral nutrition (TPN) in 19 pre-operative gastrointestinal cancer patients using a regimen previously shown to have immunorestorative properties[1]. Immunological studies included natural killer (NK) cell activity, Interleukin-2 (IL-2)-activated NK activity and lymphokine activated killer (LAK) cell activity. Non-specific lymphocyte function was assessed using a stimulation index in response to a lectin mitogen, and lymphokine (IL-2) production. Mean (±s.e.m.) values on days 0 and 7 of TPN were as follows:

	Day 0	Day 7	*t**	*P* values**
Basal NK activity (lytic units)	31·01 ± 6 6	22·7 ± 6·4	1·5	0·08 (>0·05)
Activated NK activity (lytic units)	203·7 ± 60·5	91·7 ± 11·7	1·94	0·03 (<0 05)**
LAK activity (lytic units)	23·1 ± 6·5	8·2 ± 6 1	1·87	0·046 (<0 05)**
Stimulation index	90·1 ± 14·4	70·9 ± 10·3	1·96	0·034 (<0·05)**
IL-2 production (units/ml)	195·8 ± 38·7	382 ± 192	1·15	0·13 (>0·05)

*Paired *t* test, ***P* values <0·05 regarded as significant

TPN did not significantly augment either the tumour-directed or non-specific immune response in these patients. Indeed, both activated NK activity and LAK cell production significantly deteriorated during the 7 days of TPN. These data argue against a nutritional basis for tumour-associated immunodeficiency.

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Impaired lymphokine-activated killer (LAK) cells in gastrointestinal cancer—a proliferative defect

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In vitro activation of lymphocytes with Interleukin-2 (IL-2) generates lymphoblasts (LAK cells) which are cytotoxic against tumour cells. Re-infusion of autologous LAK cells causes tumour regression in some, but not all, patients with metastases[1]. Normally LAK cells exist as precursor (Natural Killer, NK) cells which proliferate in response to IL-2 to become tumoricidal. We have measured LAK precursors (NK activity), proliferative response to IL-2, and LAK cell function in 41 control subjects, and 39 pre-operative patients with gastric or colorectal cancer (17 localized, 22 advanced). Lymphocytotoxicity against an NK target (K 562) and an NK-resistant LAK cell target (DAUDI) was measured in a ^{51}chromium release assay before and after a 3 day incubation of each subject's lymphocytes with 50 units/ml of IL-2. Lymphocyte proliferation was measured by ^{3}H-thymidine uptake. Mean values (±s.e.m.) are shown in the Table.

	Controls[a]	Localized GI cancer[b]	Advanced GI cancer[c]
Basal NK activity (per cent)	29·3 ± 2·7	36·2 ± 3·9	23·7 ± 2·7
Stimulated NK activity (per cent)	68·3 ± 3·4	66·1 ± 4·6	60·8 ± 4·4
^{3}H-thymidine uptake (cells/min × 10^{-3})	22·5 ± 2·65	19·1 ± 3·47**	11·7 ± 2·5*
LAK activity (per cent)	24·1 ± 2·6	28·8 ± 4·8**	15·3 ± 4·4*

Student's *t* test: **a versus c*, $P<0{\cdot}01$; ***b versus c*, $P<0{\cdot}01$

Thus, although patients with advanced GI cancer have normal levels of LAK precursors (basal and stimulated NK activity) their LAK cell generation is impaired. This appears to be due to failure of the precursors to proliferate and may explain why LAK cell therapy fails in some patients with GI cancer.

1. Rosenberg SA, Lotze MJ, Muul LM *et al.* Observations on the systemic administration of autologous LAK cells and recombinant Interleukin 2 to patients with metastatic cancer. *N Engl J Med* 1985; 313: 1485–92.

The clinical significance of c-myc oncogene expression in colorectal cancer

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The role of oncogenes in malignant transformation and progression is uncertain. Elevated levels of c-myc mRNA and its gene product p62$^{\text{c-myc}}$ have been detected in solid tumours and cell lines using molecular biological techniques. The ability to assess oncogene expression has been facilitated by the development of monoclonal antibodies to oncoproteins. We studied c-myc gene expression in 100 patients with colorectal cancer using the monoclonal antibody Myc 1-6E10 which recognizes p62$^{\text{c-myc}}$ in paraffin-embedded material[1]. Sections were stained using an immunoperoxidase technique, and assessed independently by two observers.

Paradoxically, staining was predominantly cytoplasmic despite the known nuclear location of p62$^{\text{c-myc}}$ due to redistribution with fixation[1]. In normal sections; maturing crypt cells and surface epithelial cells were weakly positive. All carcinomas stained positively but with varying intensity. There was no relationship between staining intensity and histological grade, Dukes' stage, DNA ploidy status, or prognosis in seventy-eight patients followed prospectively for 3 years.

We conclude that c-myc gene expression is a feature of normal maturing epithelial cells. Expression is enhanced in colorectal carcinomas and may be related to malignant transformation; but is unrelated to tumour progression or clinical behaviour.

1. Stewart J, Evan G, Watson J, Sikora K. Detection of the c-myc oncogene product in colonic polyps and carcinomas. *Br J Cancer* 1986; **53**: 1–6.

Prognosis in colorectal cancer: the surgeon still knows best

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We have prospectively studied 123 consecutive patients, presenting with colorectal cancer, from 1981 to 1983, to determine the prognostic significance of DNA ploidy status compared to conventional clinicopathological features. Tumour tissue was not obtained from four patients with clinically advanced disease, so 119 were assessed by flow cytometry, using all representative paraffin-embedded tumour blocks.

Thirty-nine patients were DNA diploid and eighty were DNA aneuploid. 'Curative' resection was achieved for 85 per cent of diploid and 65 per cent of aneuploid tumours ($\chi^2=4.03$, $P<0.05$), 6/10 Dukes' A and 33/59 (56 per cent) Dukes' B were aneuploid compared to 36/45 (80 per cent) Dukes' C ($\chi^2=6.73$, $P<0.05$).

Survival curves were constructed using the life table method and analysed using the 'Statistical Package for the Social Sciences'. The 3-year survival rate was 67 per cent with diploid tumours, compared with 35 per cent with aneuploid tumours.

Individually significant prognostic factors in decreasing order of significance were: 'Curative' resection ($\chi^2=27.62$, $P<0.001$), Dukes' stage ($\chi^2=16.43$, $P<0.001$) histological differentiation ($\chi^2=12.25$, $P=0.002$), and DNA ploidy status ($\chi^2=7.25$, $P=0.007$).

There was a significant diploid survival advantage within Dukes' B ($P=0.035$), but not within Dukes' A or C.

In a Cox regression model only 'curvative' resection, Dukes' stage and age were of independent prognostic significance, and the most powerful predictor of prognosis was the surgeon's clinical assessment regarding achievement of a 'curvative' resection.

Intact anal sphincter with end-to-end ileo-anal anastomosis for ulcerative colitis: comparison with mucosal proctectomy and pull-through anastomosis

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Our hypothesis was that an intact anal sphincter (IAS) would function better than one that had been subjected to mucosal protectomy and pull-through anastomosis. An IAS might reduce the problems of urgency, frequent defaecation and imperfect continence that may occur after mucosal protectomy (MP) with ileo-anal anastomosis (IAA).

We compared resting anal pressure (RAP), continence and frequency of defaecation in 8 patients before and 7–12 months after end-to-end stapled anastomosis (EEA) to the top of the anal canal, and in 24 similar patients after conventional MP + IAA. Each patient also had an ileal reservoir.

After EEA, RAP decreased from a median of 88 (range 60–116) to 61 (range 50–105) cm H_2O (NS), whereas after MP, RAP decreased from 81 (range 70–125) to 40 (range 22–80) cm H_2O ($P<0.001$). RAP after EEA was significantly higher than RAP after MP ($P<0.005$). Anal squeeze pressures were similar in the two groups with an EEA of 175 (range 65–170); MP 144 (range 35–250) cmH_2O (NS). All EEA patients achieved perfect continence, night and day, whereas ten of the MP patients reported some leakage at the anus ($P<0.02$). Bowel frequency per 24 h was 3.5 (range 2–6) after EEA and 5.0 (range 4–9) after MP ($P<0.05$).

Mucosal proctectomy with a pull-through anastomosis reduces RAP and impairs sphincteric function. We suggest that pull-through anastomosis should be avoided, and that the entire anal canal should be kept intact.

Bipolar diathermy versus rubber band ligation for the out-patient treatment of haemorrhoids

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We are comparing an established method for the outpatient treatment of haemorrhoids, namely rubber band ligation (RBL), with a new technique using contact bipolar diathermy (CBD), in a prospective trial.

Eighty-nine patients have been reviewed after a 3-month follow-up period (RBL = 46, CBD = 43). Both groups were similarly matched for age, sex distribution and presenting symptoms. Bipolar diathermy was administered to the base of the haemorrhoid for 3 s bursts until coagulation was achieved using a probe and BICAP 50 W generator; rubber band ligation was undertaken following the conventional technique[1].

	Number of treatments to relieve symptoms		Symptoms after first treatment			
	1	2–3	Bleeding	Prolapse	Discharge	Pain
CBD $n=43$	26	17	12	6	4	7
RBL $n=46$	20	26	18	9	3	10
P value by χ^2	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Although more patients in the RBL group required two or more treatments to achieve relief of symptoms, with bleeding and prolapse more frequent in patients undergoing RBL after initial treatment, these differences were not statistically significant (seven CBD patients and ten RBL patients experienced pain after treatment).

The initial results show that contact bipolar diathermy is a promising technique for the outpatient treatment of patients with symptomatic haemorrhoids with equivalent results to the established method of rubber band ligation, but further long-term follow-up is required.

1. Barron J. Office ligation of internal haemorrhoids. *Am J Surg* 1963; **105**: 563–70.

Exfoliated malignant cells and local recurrence of colorectal cancer

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Local recurrence following surgery for colorectal cancer occurs in 5–50 per cent of patients and is a major cause of death in this disease. It is still unclear, however, whether exfoliated cells shed during surgical resection have malignant potential and are, therefore, responsible. If such cells are viable they should grow *in vitro*.

To test this hypothesis we have studied exfoliated cell samples from 29 patients undergoing surgical resection for primary colorectal cancer. Cells were grown in mouse fibroblast monolayer culture.

Significant colonies grew from 73.9 per cent of the disaggregated primary tumours, 45 per cent of luminal washings, 45 per cent of luminal mucus samples, 5 per cent of serosal washings and 26 per cent of samples from the mesorectum (taken adjacent to, above and below the tumour). All colonies had a similar morphology, were self-limiting and regressed spontaneously after 7–10 days. Positive immunohistochemical staining with monoclonal antibodies for CEA, cytokeratin and desmosomes indicated that they were malignant cells of epithelial origin.

These studies indicate that malignant cells with proven potential for growth *in vitro* are exfoliated at surgery in patients with colorectal cancer and hence are likely to be responsible for local recurrence.

Occult blood screening for colorectal neoplasms using fecatwin sensitive and feca-eia

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We report a two-centre study of occult blood testing with fecatwin, a two-stage test using a modified guaiac resin (fecatwin sensitive), plus an enzyme-labelled immunoassay (feca-eia) which specifically detects human haemoglobin in faecal samples.

Five hundred and thirty-five patients presenting with bowel symptoms to medical and surgical outpatients were screened. The percentage compliance was 97 per cent. Patients were interviewed, given a symptom questionnaire and instructed to collect stool samples on three consecutive days. No dietary restrictions were imposed. All patients underwent sigmoidoscopy and double contrast barium enema. When the barium enema was normal and the occult blood test positive, a colonoscopy was done to exclude overlooked lesions.

Sixty-eight patients (13 per cent) had a positive reaction to both parts of the test. Of these, sixteen had colorectal carcinomas (sensitivity 0.67, specificity 0.89) and eight had adenomas (sensitivity 0.24, specificity 0.88).

Eight patients with a negative reaction to both parts of the test had colorectal carcinomas and twenty-five had adenomas.

When the guaiac test was positive in patients with colorectal carcinoma, the immunoassay was also positive. However, the immunoassay was negative in approximately half of guaiac positive patients—none of whom had serious pathology. This combination of tests significantly reduces those patients requiring further investigation.

The erythrocyte fatty acid membrane profile in patients with colorectal cancer

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Relatively small changes in the composition of cell membranes can profoundly influence cellular activity, but have been little studied in patients with colorectal cancer. Recently, it has been proposed that the ratio of stearic to oleic acid of erythrocyte membranes is reduced in patients with colorectal cancer and may be used as a sensitive diagnostic index[1]. Using gas–liquid chromatography we have determined the erythrocyte membrane fatty acid profile in 21 patients with newly diagnosed colorectal cancer and in 21 patients with benign disease matched for age and sex.

Acid	Palmitic	Palmitoleic	Stearic	Oleic	Linoleic	Arachidonic
Cancer	23·2* (21·9–24·5)	1·0 (0·6–3·5)	20·7** (19·0–21·5)	21·8* (20·0–23·4)	11·1 (10·7–12·9)	22·1 (19·9–23·6)
Control	25·4 (21·8–26·9)	1·8 (0·6–5·9)	18·6 (17·2–19·5)	20·4 (19·3–21·3)	11·8 (10·2–15·4)	23·4 (19·6–23·4)

Median (Q_1, Q_3 ranges) proportional values $^*P<0{\cdot}5$, $^{**}P<0{\cdot}005$ (Mann–Whitney *U* test)

The results (*Table*) revealed a reduced proportion of palmitic and increased proportions of oleic and stearic acids in the cancer group. Furthermore, the stearic to oleic ratio in the cancer group (0·94; 0·88–1·0) was similar to the control group (0·92; 0·87–0·96, n.s.). The palmitic to stearic acid ratio however, provided a powerful separation of those with cancer (1·11; 1·02–1·28) from those without (1·41; 1·31–1·53, $P<0{\cdot}005$).

In conclusion, this study does not support the use of the stearic to oleic acid ratio as a diagnostic tool. The significance of the alterations in fatty acid erythrocyte membrane composition in patients with colorectal cancer shown by this study is currently under investigation.

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Sutures or staples in colonic surgery?—A prospective randomized comparison

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Despite the increasing use of automated stapling techniques in gastrointestinal surgery, few attempts have been made to objectively compare them with conventional suture methods. We report the interim findings of a prospective randomized controlled trial comparing stapled and sutured anastomoses in large bowel surgery.

One hundred and fifty-eight patients, in four surgical units (one teaching unit, three district hospitals) undergoing elective ($n=134$) or emergency ($n=24$) colonic resections were randomized to receive sutured or stapled anastomoses. Bowel preparation, anti-microbial prophylaxis and anastomotic techniques were all standardized. Postoperative contrast studies were performed in patients with colo-colic or colo-rectal anastomoses.

Results, according to anastomotic site are shown below:

	Ileocolic		Colo-colic		Colorectal	
	Sutured ($n=30$)	Stapled ($n=33$)	Sutured ($n=20$)	Stapled ($n=18$)	Sutured ($n=30$)	Stapled ($n=27$)
Operation time (min) (mean ± s.d.)	107±27	92±34	123±49	91±31*	136±44	120±40
Anastomosis time (min) (mean ± s.d.)	24±12	9±5***	21±10	8±4***	29±14	18±8**
Clinical leaks	1	0	1	2	1	0
Radiological leaks	—	—	0	0	6	2

$^*P<0{\cdot}05$, $^{**}P<0{\cdot}01$, $^{***}P<0{\cdot}0001$

The incidence of symptomatic leaks was low (3·1 per cent) with no significant difference between the groups. Wound infection rate and hospital stay were also similar although anastomotic times were markedly reduced by stapling. These results suggest that sutured and stapled anastomoses provide equally satisfactory results in large bowel surgery, irrespective of the anastomotic site.

Healing and vascularity of stapled and sutured colorectal anastomoses

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Although stapling devices are widely used in low anterior resection little has been reported about the healing characteristics of these anastomoses. We have assessed experimentally six parameters of healing.

Extraperitoneal colorectal anastomoses were constructed in dogs using single layer sutures ($n=10$), two layer sutures ($n=10$), single rows of staples ($n=10$) and two rows of staples ($n=10$). The overt and radiological leak rate was 5 per cent in stapled and 40 per cent in sutured anastomoses (χ^2 test, $P<0{\cdot}05$). Major leaks occurred only in two layer suture anastomoses which also resulted in gross anastomotic narrowing (*t* test, $P<0{\cdot}05$).

Quality of healing was superior in stapled anastomoses with smaller percentage fall in hydroxyproline concentration with a mean ± s.e.m. of 2·3 ± 6·7 compared with sutured results of 23·4 ± 9·8 (*t* test, $P<0{\cdot}05$).

Bursting pressures (mmHg) were higher in stapled, 197·5 ± 20·3, than sutured anastomoses, 109 ± 24·8 (*t* test, $P<0{\cdot}05$). Histological assessment showed inferior tissue viability in two layer suture anastomoses (*t* test, $P<0{\cdot}05$).

Anastomotic vascularity was studied using three methods. Mesenteric angiography revealed in all groups superior filling of the microvasculature proximal to the anastomotic line which was confirmed by radiolabelled microsphere studies (Wilcoxon signed rank test, $P<0{\cdot}05$). Histomorphometry showed, in all types of anastomoses, higher density of microvasculature in the submucosa compared to the lamina propria (analysis of variance, $P<0{\cdot}001$).

The superior healing demonstrated in stapled anastomoses is not explained by differences in perianastomotic blood flow.

Polarographic hydrogen clearance measurement of blood flow to the muscle and mucosa of the colon in response to clamping the middle colic and caudal colic arteries in the dog

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The measurement of capillary blood flow in the large bowel could be relevant in the diagnosis and treatment of ischaemic colitis. We have developed the polarographic hydrogen gas clearance technique as described by Auckland[1] to enable measurement of blood flow in the canine colon.

Initial work involved measurement in the muscle layer of the bowel. By developing this technique further we have measured mucosal flow with contact electrodes applied from the lumen.

Four hundred and twenty-four measurements have been carried out on the muscle and mucosa of the descending colon in eleven greyhounds anaesthetized with intravenous Nembutal. Mean colon blood flow was 56·04 ± 14·5 ml/100 g in the muscle and 57·1 ± 14·2 in the mucosa and this did not change in control animals during 3·5 h of anaesthesia. Clamping the middle colic artery produced a significant fall in mucosal blood flow ($P=0{\cdot}0476$) compared to controls. However, muscle blood flow was maintained until the caudal colic artery was also occluded ($P=0{\cdot}0179$). On reperfusion, muscle flow recovered immediately while mucosal flow had not recovered at 45 min.

The technique can be used with non-flammable concentrations of hydrogen. We believe that it could be applied to patients for investigation of ischaemic bowel disorders.

1. Auckland K, Bower BF, Berliner RW. Measurement of local blood flow with hydrogen gas. *Circ Res* 1964; **14**: 164–87.

HIV (HTLVIII) and the homosexual in the surgical rectal clinic

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The rapidly rising incidence of HIV in the homosexual population poses problems with management of infected patients, both for the protection of hospital staff, and the prevention of virus transmission. Male patients under 50 years of age referred to CW during 1985 with outpatient anorectal complaints were asked about their sexual orientation, practices and venereal disease history. Homosexual patients were screened for HIV, HB$_s$Ag, and WR.

Sixty-five patients comprised 10 per cent of male outpatient referrals. Twenty-nine (45 per cent) were homosexual and thirty-six heterosexual. Most (21/25) patients with haemorrhoids were heterosexual ($\chi^2 = 5{\cdot}19$, $P < 0{\cdot}05$), and piles was the commonest diagnosis in heterosexual patients (21/36). Most (13/16) patients with anal warts were homosexual. Four of these had antibodies to HIV, one had HB$_s$Ag, and one a positive WR. Two had intra-epithelial carcinoma in the wart. Four homosexual patients had haemorrhoids; two had HIV antibodies, and one a positive WR. Eleven homosexual patients (38 per cent) carried evidence of transmissible infection, and 72 per cent had had venereal disease compared with 11 per cent of heterosexuals.

Homosexual patients should be identified at presentation because they may pose a hazard to hospital staff. Instruments require prolonged sterilization to prevent transmission of HIV or hepatitis B, and warts or tags must be examined histologically to identify carcinoma *in situ* or Kaposi's sarcoma.

Autonomic control of internal anal sphinter function

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Resting anal pressure is largely produced by internal anal sphincter (IAS) tone. The IAS is innervated by the hypogastric (presacral) nerves, deriving sympathetic innervation from the fifth lumbar segment. Stimulation of the presacral nerves in man and animals has been reported to produce both contraction and relaxation of the IAS. We have addressed this problem by carrying out intraoperative presacral nerve stimulation, measuring anal pressure in eight patients undergoing abdominal rectopexy or restorative proctocolectomy. Square wave stimuli (duration 0·5 ms, 20 pulses/s, 50 V trains) delivered to the nerves near the sacral promontory. Anal pressures were measured with a closed water-filled system.

A sharp fall in pressure was shown in seven patients (mean fall 59 cmH_2O; range 35–80 cmH_2O). Continued stimulation (90 s) was accompanied by partial recovery of anal pressure. In another patient given a β and α sympathetic blocker drug intra-operatively (labetalol 200 mg), stimulation caused a fall in anal pressure of only 15 cmH_2O.

After blocking the presacral nerves with 0·5 per cent bupivacaine, stimulating the nerves showed anal sphincter relaxation to be absent although it could still be elicited by stimulating distal to the local blocker. The rectosphincteric reflex remained intact after nerve block, and after rectal mobilization. Circumferential myotomy abolished the reflex. This reflex is therefore intramural and not transmitted via the presacral autonomics.

Neurophysiological abnormalities in female stress urinary incontinence

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In order to elucidate pelvic motor and sensory disturbances in genuine stress urinary incontinence (SUI), 28 patients were studied by modern electrophysiological techniques and compared to a control group of asymptomatic subjects. Electrical stimuli were applied to the dorsal genital nerve (DN) and urethral mucosa (UM) to measure sensory threshold. Stimulus intensity was increased to provoke reflex contraction of the striated urethral (US) and external anal sphincter (EAS) muscles and the latencies of these polysynaptic reflexes determined. Mean motor unit potential duration (MUPD) of the EAS was measured using a concentric needle electrode.

UI patients showed diminution of resting urethral sphincter EMG interference pattern and poor recruitment. There was a significant increase in DN and UM electrosensitivity in SUI patients compared with controls of mean ± s.e.m. values using Wilcoxon signed rank sum test (DN: 8·8 ± 0·78 compared with 6·05 ± 0·22 mA, $P < 0{\cdot}01$; UM: 13·8 ± 2·5 compared with 8·25 ± 0·5, $P < 0{\cdot}01$). Reflex latencies were prolonged in the patient group (DN-EAS: 49·6 ± 2·2 (3 absent) compared with 39·7 ± 1·1 ms, $P < 0{\cdot}01$; DN-U: 60 ± 2·7 (4 absent) compared with 40·5 ± 1·2, $P < 0{\cdot}01$; U-A: 83 ± 5·7 (7 absent) compared with 69·6 ± 2·1, $P < 0{\cdot}01$), SUI patients had abnormally long MUPD in the EAS (11·28 ± 0·53 ms compared with 8·66 ± 0·36, $P < 0{\cdot}01$) reflecting a neuropathy.

Using new techniques, this study demonstrates significant perineal motor and sensory deficits in SUI and explains why many patients fail to respond to conservative measures. US abnormalities are paralleled in the EAS which is a more accessible site for needle EMG studies.

Improved monitoring of renal impairment in obstructive jaundice

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Renal impairment occurs in up to 7 per cent of jaundiced patients[1] coming to surgery and may be ameliorated by a diuresis and more recently by bile salt administration[2]. A more sensitive index of renal impairment would help both to identify an 'at risk' group and to monitor therapy.

All sera are currently being batch-analysed for endotoxaemia (Toxicolor test) and preliminary results suggest significant elevations in jaundice. A second phase study compares renal function after oral bile salt therapy. Urinary N-acetyl-β-D-glucosaminidase (NAG), urinary clearance of creatinine and B_2 microglobulin (B_2MG) was measured from which was derived a 'Sieving Coefficient' independent of GFR.

We present the results in 20 jaundiced and 10 non-jaundiced surgical patients, undergoing comparable but non-hepatic abdominal surgery.

	NAG nmol h^{-1} mg^{-1} creatinine	B_2MG (ml min^{-1})	Sieving coefficient (ml min^{-1})
Pre-operative:			
Jaundice	325 ± 103·4	0·24 ± 0·5	0·66 ± 0·44
Controls	225 ± 48·3	0·30 ± 0·10	0·38 ± 0·14
Postoperative			
Jaundice	253 ± 56·8	0·65 ± 0·28	1·68 ± 0·85
Controls	165 ± 61·5	0·36 ± 0·18	0·44 ± 0·22
Significance of postoperative change in jaundiced patients	$P > 0{\cdot}05$ (n.s.)	$P < 0{\cdot}05$	$P < 0{\cdot}05$

Results expressed as mean ± s.e.m.; Student's t test

These results, the sieving coefficient in particular, show a degree of sub-clinical renal impairment in all jaundiced patients, they suggest a proximal tubular defect and may offer a sensitive index by which to monitor renal protective therapies in jaundice.

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A possible role for alkaline reflux in the development of complications of Barrett's oesophagus

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Patients with a columnar-lined (Barrett's) oesophagus may present with, or develop, complications such as ulceration, stricture or neoplasia. Such complications may involve further insult to the mucosa than acid injury alone. To assess the possible role of alkaline reflux in the development of complications in Barrett's oesophagus, eighteen patients with Barrett's oesophagus had fasting and post-prandial (modified LUNDH test meal) intragastric bile acid concentrations estimated. Eleven patients had complications of Barrett's (CB) and seven had uncomplicated Barret's (UB). There were seven strictures—one of whom had severe dysplasia, three had Barrett's ulcers—one with a stricture and one with an adenocarcinoma in the Barrett's mucosa in the CB group.

The results (μM/l) showing median and (range) were as follows:

Bile acid concentration μM/l	Fasting	Postprandial 20 min	40 min	60 min	90 min	120 min
Controls	22	47	40	75**	55*	35*
$n=9$	(0–109)	(0–3137)	(0–398)	(0–122)	(0–339)	(0–326)
CB	25	25	187	420	290	366
$n=11$	(0–291)	(0–2692)	(0–1417)	(87–1188)	(0–1090)	(0–1200)
UB	0	17	17	40**	85*	140*
$n=7$	(0–266)	(0–184)	(0–184)	(0–278)	(0–440)	(0–311)

*$P<0{\cdot}05$; **$P<0{\cdot}01$; Wilcoxon Rank sum test: significantly different

The CB group had intragastric bile acid concentrations which were significantly increased at 1 h, and maintained for up to 2 h postprandially in comparison to the UB group and the control group.

Alkaline reflux may be implicated in the development of complications in Barrett's oesophagus.

A multicentre prospective trial of low-volume fresh frozen plasma therapy in acute pancreatitis

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An uncontrolled clinical study and animal work suggest that fresh frozen plasma (FFP) reduces mortality in acute pancreatitis, possibly by replenishing the plasma antiprotease system. A prospective controlled randomized clinical trial is underway to explore this possibility.

Patients with acute pancreatitis have their 'Glasgow multiple prognostic criteria' recorded and are randomized to receive either FFP (2 units per 24 h for 72 h) or human albumin solution (1 bottle per 24 h for 72 h). Serum α_1 antiprotease and α_2 macroglobulin levels are measured on days 1, 3 and 7.

To date, 156 attacks of acute pancreatitis have been randomized equally to FFP and colloid control. The two groups are well matched in all clinical criteria including predicted severity of pancreatitis.

No significant difference has been shown between the two groups in terms of clinical outcome. Both show a significant rise in α_1 antiprotease levels from days 1 to 3 ($P<0{\cdot}0001$) and this is not influenced by administration of FFP. α_2 Macroglobulin levels are reduced in both groups on day 1 and show a significant fall in the colloid group from days 1 to 3 ($P<0{\cdot}05$) but remain substantially unaltered in patients receiving FFP ($P=0{\cdot}91$, two-tailed Mann–Whitney ranking test).

Relatively low volumes of FFP have been shown to reduce the fall in serum α_2 macroglobulin levels in acute pancreatitis and this may have therapeutic implications.

Post-resectional changes in plasma enteroglucagon mirror crypt cell production rates in defunctioned small bowel

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Post-resectional hyperplasia seen in a Thiry–Vella fistula (TVF) implicates a humoral stimulus to intestinal adaptation. Enteroglucagon is produced mainly in distal small bowel (and also colon) and therefore jejunal resection might be expected both to stimulate adaptive change in a TVF and raise plasma enteroglucagon levels more than an equivalent ileal resection.

This hypothesis was treated in Sprague–Dawley rats ($n=40$) given a TVF of the mid-60 per cent of the small intestine. One group had concomitant resection of the jejunum proximal to the TVF (JR; $n=12$), another had resection of the ileum distal to the TVF (IR; $n=13$), while controls had no further procedure ($n=15$). Enteroglucagon levels were measured on the day of operation and also at sacrifice 10 days later when the crypt cell production rate (CCPR) in the centre of the TVF was determined.

JR produced an 81 per cent increase in CCPR over control values ($28{\cdot}5\pm4{\cdot}2$ *versus* $15{\cdot}8\pm2{\cdot}3$ cells crypt^{-1} h^{-1}: $P=0{\cdot}025$) whereas IR had no demonstrable effect ($17{\cdot}5\pm2{\cdot}3$ cells crypt^{-1} h^{-1}). Plasma enteroglucagon levels were raised by JR from $82{\cdot}6\pm9{\cdot}5$ to $276{\cdot}9\pm26{\cdot}0$ pmol/l ($P=0{\cdot}0001$), and on the tenth postoperative day were higher than both controls ($131{\cdot}4\pm10{\cdot}2$ pmol/l: $P=0{\cdot}025$) and IR ($123{\cdot}3\pm30{\cdot}7$ pmol/l: $P=0{\cdot}025$).

In conclusion IR caused no significant changes in enteroglucagon. Adaptive hyperplasia in isolated small bowel is modulated by enteroglucagon which is released from the distal small intestine following jejunectomy.

Gallbladder function and fasting enterogastric bile reflux

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Enterogastric reflux (EGR) of bile is common after gastric surgery and may cause other symptoms. The gallbladder regulates bile flow, yet data concerning the relationship of GB function to EGR is scanty.

In this study, 291 patients with dyspepsia were investigated in the fasting phase of a gallbladder function and EGR by ^{99m}Tc-E Hida isotope scan. This isotope concentrates in bile. Following injection of ^{99m}Tc-E Hida, sixty 1 min images were taken by gamma camera and stored on computer. Re-run of these images in cine mode demonstrated concentration of isotope in the BG, drainage into duodenum and reflux into stomach (EGR). In all patients, the incidence of previous gastric surgery was noted.

Gallbladder function was present in 169 and absent in 122 patients, of whom 47 had had a previous cholecystectomy. Enterogastric reflux (EGR) was shown in 82 patients of whom 10 had had previous gastric surgery. A non-functioning gallbladder was associated with a high incidence of EGR (*Table*).

	Gallbladder function Present	Absent
EGR + no gastric surgery	29 (20%)	43 (40%)*
EGR + previous gastric surgery	5	5
No EGR	135	74

*$P<0{\cdot}005$: χ^2 test

We concluded that a high incidence of EGR which does not result from previous gastric surgery occurs in patients with a non-functional gallbladder. EGR may account for some postcholecystectomy symptoms.

A non-invastive, endoscopic technique to measure gastrointestinal blood flow

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Changes in mucosal blood flow may occur in many gastrointestinal disorders, but assessment is impossible without a non-invasive *in vivo* technique. We have compared endoscopic laser Doppler (LD) with oxygen electrode (OE) measurements in a dog isolated colon preparation, using variable perfusion measured with an electromagnetic flow probe.

At maximum flow, LD measurements were made at three sites to compare mucosal with serosal readings. Flow rate was varied (1–38 ml/min) and measurements of microcirculatory flux obtained using LD and of oxygen tension using a serosal OE.

In the upper colon the serosal value of $46{\cdot}8\pm18{\cdot}7$ V (mean ± s.d.) was similar to that of $41{\cdot}1\pm18{\cdot}2$ V on the mucosa. Both values rose in mid-colon (serosa $52{\cdot}6\pm17{\cdot}9$ V, mucosa $45{\cdot}7\pm15{\cdot}2$ V) and a further similar increase occurred in the distal bowel (serosa $61{\cdot}3\pm17{\cdot}6$ V, mucosa $54{\cdot}1\pm15{\cdot}1$ V).

LD serosal readings correlated significantly with EM flow ($r=0{\cdot}544$, $0{\cdot}01>P<0{\cdot}001$). A similar linear correlation was observed between OE values and EM flow ($r=0{\cdot}650$, $P<0{\cdot}001$). Oxygen tension measurements varied as expected with microcirculatory flux ($r=0{\cdot}441$, $0{\cdot}02>P<0{\cdot}01$).

Endoscopic laser Dopper assessment of colonic microcirculation accurately reflects changes in colonic blood flow.

The role of small bowel resistances and osmoreceptor feedback in gastric emptying after truncal vagotomy and pyloroplasty

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After truncal vagotomy and pyloroplasty (TV + P) gastric emptying (GE) of liquids is biphasic, with rapid early GE often inducing post-vagotomy symptoms[1]. Factors restricting this early phase of GE and provoking transition to the second, slow phase are unknown. We investigated the contributions to GE of small bowel resistances, osmoreceptor feedback and sympathetic inhibitory reflexes to small bowel distension.

Sixty GE studies were performed, using gamma camera imaging of radiolabelled 15 per cent dextrose, in six dogs with TV + P and fitted with proximal duodenal cannulae. With the cannula closed GE was initially rapid, followed by stasis. Opening the cannula produced precipitous GE. Distal duodenal instillation of 15 per cent dextrose, at a rate equivalent to GE with the cannula closed, failed to restore GE to normal post-vagotomy values, although it was slower than with diversion alone. Normal saline instillation had no effect on precipitous GE. Percentage amounts emptied were as follows:

	Cannula closed		Open + 15% dextrose instillation		Open + no instillation		Open + saline instillation
15 min	32±5·3	n.s.	50±7·0	*	76±4·2	n.s.	78±10·6
30 min	31±4·3	*	56±5·7	**	85±2·9	n.s.	86±7·2
60 min	34±4·8	**	65±6·8	*	88±2·6	n.s.	90±5·4

mean ± s.e.m. $^*P<0·05$, $^{**}P<0·01$, between adjacent columns (ANOVA)

These results indicate that, following TV + P, small bowel resistances play a significant role in controlling GE. Osmoreceptor responses persist after TV + P, but sympathetic inhibitory responses are not invoked. The results contrast with those from the vagally intact model[2]. A failure to generate small bowel resistances may determine the development of post-vagotomy symptoms.

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The manometric features of the oesophageal body in patients with oesophagitis

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The association between gastro-oesophageal reflux and oesophageal motility has been investigated[1,2] but the precise defects have been incompletely defined[3] and it is unclear whether these predispose to, or result from oesophagitis.

A detailed manometric study was undertaken in 48 patients with endoscopic oesophagitis by a technique allowing analysis of peristaltic activity after wet and dry swallows at segmental levels in the oesophagus. Twenty asymptomatic volunteers served as controls.

Peristaltic amplitude was lower in patients than controls ($P<0·001$), this reduction occurring in the distal two-thirds for both wet and dry swallows ($P<0·01$) and in the upper third for dry swallows only ($P<0·05$), these changes being independent of the degree of oesophagitis. Wave velocity was reduced in the lower two-thirds for wet swallows and the upper two-thirds for dry swallows in patients with severe oesophagitis ($P<0·05$) but the presence of oesophagitis had no effect on wave duration ($P>0·05$). Secondary peristaltic activity and abnormal wave forms occurred in the presence of severe oesophagitis ($P<0·01$).

Manometric abnormalities associated with oesophagitis exhibit two components, one of which is independent of, and the other related to the degree of oesophagitis, which may reflect multifactorial aetiology.

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Can the results of antireflux surgery be predicted by early oesophageal pH monitoring?

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Prolonged oesophageal pH monitoring can be used to assess the results of anti-reflux surgery (ARS). The optimum timing of postoperative monitoring is controversial. The aim of this study was to investigate whether there is a change in the pH results recorded at 1 week and 3 months after ARS and whether early monitoring may have a predictive value.

Studies were performed on fifteen patients (mean age 51 years) 1 week and 3 months following trans-abdominal ARS. A glass pH probe (Microelectrode Inc.) was positioned 5 cm above the manometrically determined lower oesophageal sphincter and connected to an ambulatory pH recording system (Ormed). The recording period was 22 h. Percentage reflux time (total, erect and supine) and reflux episodes (total number, number longer than 5 min and longest episode) were analysed at pH values 3, 3·5, 4, 4·5 and 5 and were compared by the paired '*t*' test and simple linear regression analysis for both groups.

There was no significant difference ($P<0·05$) between the corresponding values at 1 week and 3 months. There was significant correlation ($P>0·05$) for total reflux time and reflux episodes longer than 5 min at pH values 3·5 and 4. For the remaining four factors there was good correlation for supine reflux time, total number of reflux episodes and longest reflux episodes at pH values 3·5 and for erect reflux time at pH value 4.

We conclude that there is no difference in results of pH testing at 1 week or 3 months after ARS and that early assessment at pH levels 3·5 and 4 may be used to predict the later results.

The susceptibility of the gastric mucosa to injury in portal hypertension

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Experimental studies suggest that passive congestion of the gastric mucosa in portal hypertension increases its susceptibility to injury[1]. It is well documented, however, that splanchnic arterial flow is increased in portal hypertension. We have developed a rat model of portal hypertension by creating a calibrated portal vein stenosis (PVS) where the independent effect of differing levels of portal venous pressure (PVP) can be compared with the degree of gastric mucosal injury.

Three days following portal vein stenosis PVP was 17·2 ± 1·9 mmHg (mean ± s.e.m.) compared with 8·0 ± 0·3 in sham operated (SO) controls. Pressure fell to 14·8 mmHg at 1 week and 11·3 mmHg at 4 weeks following stenosis. During this time portosystemic shunting, measured with γ-labelled microspheres[2], rose from 24·6 per cent to 59·6 per cent in the stenosis groups. Alcohol (2 ml, 60 per cent) was given to animals at all three time intervals by lavage and gastric lesion score documented by an independent observer.

In the 3 day group, lesion score was 194·7 ± 20·1 in the SO group ($n=20$) compared to 55·4 ± 24·6 in the group ($n=21$) with portal hypertension ($P<0·001$). This significant difference persisted at weeks 1 and 4.

This model of portal hypertension renders the gastric mucosa less susceptible to injury by exogenous agents.

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Which bile salt for the jaundiced patient?

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Postoperative renal failure still occurs in 9 per cent of jaundiced patients undergoing surgery, and is associated with circulating systemic bacterial endotoxin. Pre-operative administration of sodium deoxycholate has been shown to prevent endotoxaemia and protect renal function[1], but ursodeoxycholic acid is ineffective[2].

A comparative study of bile salts has thus been performed. Bile salts were incubated with endotoxin *in vitro*, and resultant endotoxin activity measured by a chromogenic Limulus test. Endotoxin absorption from the gut was measured in bile duct ligated rats after 48 h of oral bile salt administration, using radiolabelled endotoxin.

It was found that the *in vitro* and *in vivo* activities of bile salts related to their detergent properties. Deoxycholate was the most potent *in vitro* and *in vivo*. The second most effective was chenodeoxycholic acid, but ursodeoxycholic acid was least effective. Systemic endotoxaemia and renal function were measured in 12 jaundiced patients given chenodeoxycholic acid for 48 h pre-operatively and compared with 22 jaundiced controls. Endotoxaemia developed in 50 per cent and renal impairment in 25 per cent of the treated group.

Sodium deoxycholate is the only bile salt which has been shown to prevent both endotoxaemia and renal failure in jaundiced patients[1].

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Biliary gastritis is associated with altered mucosal cell kinetics

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Since bile reflux has been implicated in the reported increased incidence of cancer in the postoperative stomach, and because bile reflux results in distinct histological changes which can be graded to give a 'reflux score' of 0–15[1], we have examined the relationship between mucosal cell kinetics and the histological changes that accompany bile reflux.

Multiple gastric biopsies were taken from patients with normal endoscopic findings ($n=10$), duodenal ulceration ($n=10$), gastric ulceration ($n=8$), or clinical and endoscopic evidence of bile reflux secondary to prior gastric surgery ($n=12$). The thymidine labelling index (TLI) and 'reflux score' of the biopsies were determined.

The TLI and 'reflux score' were significantly higher in the postoperative group ($P<0{\cdot}01$) when compared with the other three groups (Mann–Whitney U test). There was a statistically significant correlation ($P<0{\cdot}10$) between 'reflux score' and TLI (Spearman rank correlation test).

	Reflux score (Mean and range)	TLI (Mean and range)
Normal	8·8 (5–10)	24·6 (22–27)
Duodenal ulceration	7·6 (5–10)	23·9 (20–28)
Gastric ulceration	8·0 (5–11)	23·2 (20–27)
Postoperative patients	11·5 (8–15)	31·0 (39–55)

The high TLI in patients with reflux was associated with considerable expansion of the proliferative zone.

These results suggest that the histological changes of bile reflux gastritis are accompanied by significant alterations in gastric mucosal kinetics. These changes may be of relevance in the reported association between bile reflux and gastric cancer.

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Maintenance Ranitidine prophylaxis after haemorrhage from a duodenal ulcer—a 2 year study

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Forty patients who had a healed duodenal ulcer which initially presented with haemorrhage were entered into a blind, randomized study of maintenance Ranitidine therapy (150 mg *nocte*) *versus* a placebo preparation to determine whether or not Ranitidine can reduce the incidence of further ulceration and haemorrhage in this group of patients. All study patients were regularly reviewed by interview and endoscopy until either endoscopic evidence of recurrent duodenal ulceration was obtained or a 2-year ulcer-free follow-up was completed.

Twenty-four of the forty patients (60 per cent) developed further duodenal ulceration during the 2-year study period, but recurrence was only associated with bleeding in two cases (9 per cent) of recurrences: 5 per cent of total group). Maintenance Ranitidine therapy was found to significantly reduce the incidence of further duodenal ulceration at all time intervals beyond 3 months, the maximum protective effect being observed after 12 to 15 months of treatment ($P<0{\cdot}001$). Thereafter the difference became less striking although still statistically significant at 2 years ($P<0{\cdot}05$). It was noted that 81 per cent of placebo patients had symptoms at the time of ulcer recurrence compared to only 25 per cent of Ranitidine patients ($P<0{\cdot}03$).

While maintenance Ranitidine therapy may provide significant protection against further duodenal ulceration in this situation over the time period studied, the implications of the observed high asymptomatic recurrence rate in the Ranitidine group require further evaluation.

The edrophonium provocation test in the diagnosis of diffuse oesophageal spasm

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Diffuse oesophageal spasm (DOS) was diagnosed in 30 out of 350 patients (8 per cent) referred to an oesophageal laboratory. Because of the intermittent nature of the symptoms, edrophonium was used as a provocative agent to increase diagnostic yield. Our criteria for DOS are dysphagia or chest pain, or both, with manometry showing retention of peristalsis, more than 30 per cent synchronous contractions in response to wet swallows and contractions of amplitude greater than 200 mmHg and duration of more than 7 s.

All patients underwent transnasal manometry using a Gaeltec system of six internal transducers arranged at 5 cm intervals from the catheter tip. Twenty-six patients received 10 mg of edrophonium as an intravenous bolus. Reproduction of symptoms with typical manometry of DOS indicated a positive provocation test. There were no significant side effects.

	Edrophonium positive	Edrophonium negative	No edrophonium	Total number
Manometry positive	9	8	4	21
Manometry negative	9	0	0	9

Without edrophonium provocation testing 30 per cent of patients would not have been diagnosed as diffuse oesophageal spasm.

Surgery for haemorrhage from gastric ulcers

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Surgery for bleeding gastric ulcer (GU) remains controversial. The aim of this study was to analyse retrospectively the effects on mortality and morbidity of different operations for this condition.

During the period between 1977 and 1985, simple undersewing of bleeding ulcers has replaced more extensive procedures in the practice of some surgeons in our institution. Sixty-one patients required surgery for bleeding GU during this time. All operations were performed by consultants or experienced senior registrars. Mean age, interval between admission and surgery and pre-operative transfusion requirements were similar for all groups of patients.

Mortality was highest in the groups who had undersewing plus vagotomy and drainage and lowest in the undersewing alone group (*Table*).

	Number	Deaths	Mortality
Partial gastrectomy	19	5	26%
Undersewing + vagotomy + drainage	22	10	46%*
Undersewing alone	20	2	10%*
All	61	17	28%

* $P<0{\cdot}02$

Follow-up of patients in the undersewing alone group, which ranged from 1 month to 7 years (mean 20·5 months), demonstrated two recurrent ulcers; one of these bled and was again treated by undersewing while the other was managed by medical therapy.

These results suggest that undersewing alone may be the procedure of choice for bleeding gastric ulcers.

Transcutaneous oxygen tensions (tcP_{O_2}) as a prognostic indicator and measure of treatment of recurrent venous ulceration

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Skin hypoxia secondary to pericapillary fibrin deposits may be important in the development of venous ulcers[1]. This is supported by the demonstration of low tcP_{O_2} in patients with venous insufficiency[2]. If low tcP_{O_2} is important, it would be expected that tcP_{O_2} should be lower in limbs which re-ulcerate than in those that remain healed, and treatment that improves liposclerosis should increase tcP_{O_2}.

We have studied 53 patients with recently-healed venous ulcers. A Radiometer electrode at 45°C was used to measure tcP_{O_2} at the healed ulcer site, 7·5 cm above the medial malleolus on both legs, and also the upper arm. The results were expressed as a ratio of the reading at the involved site to the reading at the arm. Treatment was randomized to elastic stockings and stanozolol or elastic stockings and surgical ablation of superficial veins and incompetent communicating veins.

There was no significant difference between the tcP_{O_2} measurements of limbs that remained healed and those that re-ulcerated ($P=0·10$, ulcer site; $P=0·28$, liposclerotic area). TcP_{O_2} measured at the liposclerotic area was significantly increased 12 months after both forms of treatment.

	tcP_{O_2} ratio (±s.d.)			
	Ulcer site		Liposclerotic area	
	Surgery	Stanozolol	Surgery	Stanozolol
At healing	0·30±0·20	0·26±0·19	0·77±0·26	0·59±0·26
12 months	0·53±0·21	0·40±0·28	0·92±0·22	0·76±0·25
	$P=0·125$	$P=0·23$	$P<0·05$	$P=0·04$

We concluded that tcP_{O_2} measured immediately after healing of a venous ulcer is not a good prognostic indicator for recurrent venous ulceration, but that tcP_{O_2} measured at the liposclerotic area is increased after both forms of treatment.

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Measurement of the healing of venous ulcers

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The time required for venous ulcers to heal has been thought to be related to the initial ulcer size. Stereo photogrammetry[1] and computerized ultrasonic digitized area measurements using a light pen[2] are new and expensive techniques that have been compared with simpler measurements of surface area of leg ulcers.

In this study, we have calculated the surface area of 99 ulcers by two methods: (i) the product of two perpendicular diameters of the ulcer surface[1], (ii) photographing the ulcers and using a computerized ultrasonic digitized area measurement[2].

A correlation coefficient of 0·9513 ($P<0·0001$) was obtained. This correlation remained good throughout all stages of ulcer healing. A poor correlation was found between the initial ulcer size and the time to total healing. There was also a poor correlation between healing rates during selected time intervals and the overall healing rate. In a large placebo controlled, double blind study ($n=74$), we found that the time to total healing was similar for the two treatment groups (control group: 76 per cent healed at 12 months; treatment group: 87 per cent healed at 12 months).

We conclude that simple measurement of the maximal widths of an ulcer is an easy and accurate method of monitoring treatment, and that time to total healing of the limb is the only accurate method of evaluating the clinical benefit of new treatments for venous ulcers.

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2. Coleridge Smith PD, Scurr JH. A direct method for measuring venous ulcers. *Br J Surg* 1986; 73: 320.

Day case grafting of chronic venous ulcers

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Venous ulcers are common, often resistant to therapy and need regular dressings thus placing a heavy financial burden on the health service[1]. Skin grafting speeds healing of larger ulcers and may be performed on out-patients making considerable savings[2]. We have compared healing rates of venous ulcers treated as out-patients by meshed split skin or pinch skin grafting.

Following preparation to healthy granulation tissue, 32 venous ulcers larger than 10 cm and previously unhealed for a mean of 2·3 years were randomized to receive pinch grafts or meshed split skin graft (mesh graft cutter, Downs Surgical Ltd) performed under local anaesthetic as out-patients. A standard graduated compression bandage was applied and changed weekly when healing was assessed from area measurements by direct tracing.

		Healing rate (cm^2/week)		Fully healed at	
	Size (cm^2)	First 2 weeks	Next 4 weeks	4 weeks	12 weeks
Mesh graft ($n=16$)	27·5±7·4	8·6±2·4	2·1±0·8	6	10
Pinch graft ($n=16$)	25·4±4·7	6·0±1·6	1·8±0·5	4	7

All results expressed as mean±s.e.m.

More than half the ulcers healed within 12 weeks but there was little difference in healing rate between pinch and meshed skin grafts. With meshed grafts, more ulcers were fully healed but the difference was statistically insignificant.

Large venous ulcers may be rapidly healed as out-patients by simple skin grafting methods using either pinch or meshed split skin.

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Is the post-phlebitic limb always post-thrombotic?

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The term 'post-phlebitic syndrome' implies a previous history of deep venous thrombosis. To test the validity of this assumption, 106 patients who had routine postoperative bilateral ascending venography following total hip replacement were reviewed 5 years after surgery.

Patients were assessed clinically for symptoms and signs of the 'post-phlebitic syndrome' (pain, swelling, induration, pigmentation, ulceration and varicose veins). Haemodynamic changes were assessed by foot volumetry and an objective score was derived by computer analysis.

Twenty-six patients (25 per cent) had postoperative DVT. Fifty per cent of all patients had at least one symptom or sign of the post-phlebitic limb. Pain was present in 9 limbs; swelling in 13; induration in 18; pigmentation in 55 and varicose veins in 39 limbs.

At 5 years there was no significant difference in the incidence of symptoms, signs or haemodynamic changes of the 'post-phlebitic syndrome' between limbs with or without a previous DVT. We conclude that deep vein thrombosis is not the only factor involved in the aetiology of the post-phlebitic limb.

Common carotid blood velocity and cerebrovascular symptoms

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Peak systolic blood velocity (PSV) can be accurately measured with duplex scanning by mid-stream pulsed Doppler sampling at known angle.

The relationship between intracerebral symptoms and the PSV of the common carotid artery (CCA) was studied in 1336 patients. Past cerebrovascular accident (CVA) in 260 patients was associated with significant reduction in PSV both ipsilateral, $P<0.0003$, and contralateral, $P<0.05$ (Student's t test). Past transient ischaemic attack (TIA) in 365 patients was associated with lower ipsilateral velocity ($P<0.02$) but there was no significant difference in contralateral velocity ($P>0.3$).

Inhalation of 4 per cent carbon dioxide was used to augment the cerebral flow in a further 22 patients without knowledge of their symptoms. One CCA occlusion and 21 ICA stenoses greater than 50 per cent were in this group. There were no ipsilateral symptoms in 21 sides that increased CCA velocity after CO_2. Of 22 sides with reduced or unchanged CCA velocity, 10 had ipsilateral symptoms (χ^2 test$=10.02$, $P<0.01$). Within 1 year a further four patients developed cerebrovascular symptoms, all of whom had reduced CCA velocity, three ipsilateral and one contralateral.

The findings suggest that hemispheric symptoms (TIA or CVA) are associated with reduced CCA velocity and abolition of CO_2 augmentation. Abnormal CO_2 reactivity, may prove useful in identifying high-risk patients, some before onset of symptoms.

Plaque morphology determined by Duplex—is it relevant?

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Non-invasive studies of the internal carotid artery (ICA) concentrate on assessing percentage stenosis, although this does not correlate with symptoms or risk of stroke. This study prospectively assessed the accuracy and usefulness of Duplex ultrasonography in defining plaque appearance.

In 12 months 58 patients with ICA stenosis were assessed by Hoffrel (518 FD) Duplex scanning, and plaque defined as heterogeneous, suggestive of intraplaque haemorrhage, or homogeneous.

Experiment 1: pre-operative Duplex findings were compared with histological evidence of haemorrhage (Perl's and Martius Blue stains) in 21 endarterectomy specimens (*see Table 1*).

Table 1

		Histology	
		Haemorrhage	No haemorrhage
Duplex	Heterogeneous	13	3
	Homogeneous	2	3

Duplex has a sensitivity of 87 per cent, specificity of 50 per cent and positive predictive value of 81 per cent for intraplaque haemorrhage.

Experiment 2: excluding normal and occluded vessels, 88 carotid plaques were classified as heterogeneous or homogeneous. Plaque morphology was correlated with symptoms of ipsilateral cerebral hemispheric ischaemia (*Table 2*).

Table 2

		Ipsilateral cerebral hemisphere	
		Symptomatic	Asymptomatic
Duplex	Heterogeneous	19	8
	Homogeneous	27	34

Heterogeneous plaques were more likely to be associated with ipsilateral cerebral symptoms (χ^2 test$=4.2$, $P<0.05$). Duplex ultrasonography accurately identified intraplaque haemorrhage, which was associated with ipsilateral ischaemic symptoms. Plaque appearance on ultrasound assists selection of patients for carotid endarterectomy.

The effect of defibrinogenation on the early patency of small calibre arterial grafts

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Defibrinogenation with Arvin was studied in a new animal model which closely simulates the clinical problem of a narrow arterial graft into a poor run-off. A 3 mm internal diameter PTFE graft was inserted into a rabbit abdominal aorta and the distal run-off was reduced by narrowing both common iliac arteries using special clips which reduced the graft flow by 50 per cent. This model was studied in 29 animals, 14 of which received Arvin in single subcutaneous daily doses of 20 units/kg body weight, starting 2 days before surgery and continuing for 2 days postoperatively.

The peroperative fibrinogen level was 2.8 ± 0.9 g/l in the controls compared to 0.4 ± 0.3 g/l in the treated group. The degree of defibrinogenation in these animals produced no problems with haemostasis. The cumulative patency rates in the controls at 24 h, 48 h and 4 days were 43 per cent, 28 per cent and 28 per cent while in the Arvin group they were 86 per cent ($P<0.05$), 73 per cent ($P<0.05$) and 73 per cent ($P<0.05$) respectively. All grafts patent at 4 days remained patent until the animals were sacrificed 1–4 weeks later.

Therefore in this model of a narrow PTFE graft with a poor run-off, defibrinogenation was a safe and effective method of improving the early patency. On the basis of this study, a multicentre clinical trial has been started in patients at high risk of early graft thrombosis.

The effect of dopamine on renal function during aortic cross-clamping

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Infra-renal aortic cross-clamping profoundly affects renal haemodynamics for up to 1 hour post-declamp[1].

In unanaesthetized dopamine infusion (1–10 μg kg^{-1} min^{-1}) increases renal blood flow, GFR and sodium excretion. The effect of dopamine (2 μg kg^{-1} min^{-1}) upon renal function during aortic surgery was studied. Dopamine was infused either prior to cross-clamping ($n=9$) or synchronously ($n=9$). Hartman's solution (15 ml kg^{-1} h^{-1}) was given throughout surgery and measured blood loss was replaced. Estimations were made of urine flow rate, creatinine clearance, sodium excretion and plasma renin.

The pre-clamp Hartman's infusion period was taken as the baseline value. Dopamine infusion was associated with highly significant increases in all the parameters studied ($P<0.05$) before, during and after aortic cross-clamping.

We conclude that dopamine infusion during aortic cross-clamping counters the reported alteration in renal haemodynamics and offers potential benefits to patients undergoing aortic surgery who have impaired renal function.

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An investigation into the mechanism of giant cell formation by monocytes from patients with breast cancer

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We have recently demonstrated that monocytes from patients with breast cancer form giant cells (GC) when cultured *in vitro*[1]. The aim of the present study was to investigate in more detail the factors responsible for this phenomenon.

Monocytes from women with primary breast cancer or from age-matched healthy volunteers with no evidence of breast cancer were separated and purified over Ficoll–Hypaque and discontinuous Percoll density gradient. The separated monocytes were incubated for 6 days. Following incubation, the cells and the supernatant culture medium were examined by electron microscopy. Reverse transcriptase activity was assayed in the supernatant.

Electron microscopical examination of the monocytes revealed the presence of particles (100 nm diameter) near the periphery of the cells. These particles were of similar appearance to retroviral particles present in mouse mammary tumour cell lines. They were also present in the supernatant culture medium of the monocytes and were characterized by the presence of a double-layer, characteristic of viral particles. Reverse transcriptase was positive in the supernatant in seven out of eight patients with breast cancer, and negative in all controls. The results of this study are suggestive of the presence of a retrovirus in monocytes of patients with breast cancer, although their significance in the pathyphysiology of the disease has yet to be established.

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A prospective study of anxiety and depression in patients (and husbands) with breast cancer given a choice of mastectomy or wide excision

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Survival and disease-free interval is similar after both mastectomy and axillary clearance (M) and wide excision, axillary clearance and radiotherapy (WE) for early breast cancer[1]. We have prospectively studied anxiety and depression in two groups of patients with T_1/T_2 breast cancer. One group of patients ($n = 20$) were given a choice of M or WE. The other group ($n = 10$) received mastectomy because of central tumours. Levels of anxiety and depression were recorded[2] in both patients and their husbands both pre-operatively and at 2-monthly postoperative intervals.

Table 1 *Anxiety study*

	Pre-operative		Postoperative	
	Patient	Husband	Patient	Husband
Given choice ($n = 20$)	8·0*	7·0*	5·0*	2·0*
	(0–18)	(0–12)	(0–9)	(0–7)
Not given choice ($n = 10$)	13·5	13·0	5·5	7·0
	(3–20)	(10–19)	(1–17)	(3–13)

Table 2 *Depression study*

	Pre-operative		Postoperative	
Given choice ($n = 20$)	2·0*	3·0*	1·0*	1·0*
	(0–10)	(0–7)	(0–5)	(0–4)
Note given choice ($n = 10$)	2·0	8·0	1·0	4·0
	(0–16)	(3–12)	(0–14)	(1–16)

All medians with ranges in parentheses *$P < 0{\cdot}01$. Given choice *versus* Not given choice

Both patients (and husbands) who were not given a choice of treatment were significantly more anxious and depressed both pre- and postoperatively compared with those given a choice. The latter group had similar psychological morbidity to general surgical control patients without cancer. Anxiety and depression were not related to SM or WE. Psychological morbidity of both women and husbands is reduced after pre-operative involvement in decisions concerning treatment for early breast cancer.

1. Fisher B, Bauer M, Margolese R *et al.* Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Eng J Med* 1985; **312**: 665–73.
2. Zigmund A, Snaith R. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavia* 1983; **67**: 361–70.

Inhibition of oxygen free radical production ameliorates acute stress ulceration in the rat

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Recent evidence suggests that oxygen free radicals may play a role in acute gastric mucosal damage following injury[1]. Soybean trypsin inhibitor (STI) has been shown to prevent conversion of xanthine dehydrogenase to the free radical producing xanthine oxidase and to ameliorate reperfusion injury in the feline intestine, following ischaemia. Using a haemorrhagic shock and intragastric acid model of stress ulceration in the anaesthetized rat, we investigated the effect of STI on gastric mucosal damage. Five minutes following intragastric instillation of 1 ml 0·1 M HCl/100 g and immediately before haemorrhagic shock. STI 15 mg/kg was given intravenously ($n = 6$). Control rats ($n = 8$) received an equal volume of 0·9 per cent saline. Transmucosal gastric potential difference (PD) was measured continuously throughout the experiment.

The area of gastric ulceration was expressed as a percentage of the total area of corpus and antrum. In the control group, gastric ulceration was 13·7 ± 3·6 (percentage total area) compared to 3·3 ± 1·1 (percentage total area) in the STI group ($P < 0{\cdot}02$). Data from potential difference measurements were:

	Baseline	20 min post-haemorrhage	20 min post-transfusion
Control (mV)	−33·9 ± 0·9	−6·6 ± 2·2*†	−17·2 ± 4·0
STI (mV)	−35·2 ± 1·7	−20·3 ± 4·7*	−32·4 ± 4·8

Values are mean ± s.e.m. * $P < 0{\cdot}005$ *versus* baseline. † $P < 0{\cdot}02$ *versus* STI

We conclude that STI significantly ameliorates gastric mucosal injury induced by haemorrhagic shock, possibly by inhibition of oxygen free radical formation. The reduction in mucosal injury is reflected in the PD measurements.

1. Itoh M, Guth PH. Role of oxygen-derived free radicals in ischemic gastric injury in the rat. *Gastroenterology* 1985; **88**: 1162–67.

Trial without catheter following acute retention of urine

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Acute urinary retention in men is usually managed by insertion of a urethral catheter. This may be removed to ascertain whether micturition can be re-established (trial without catheter), sparing some patients further intervention, but causing others discomfort or harm. This study was performed to establish whether this practice is justified.

Sixty patients with acute urinary retention were randomly allocated into three groups: catheters were removed immediately, 24 h or 48 h later.

Seventeen (28 per cent) urinated satisfactorily after removal of the catheter. Re-establishment of successful micturition was unassociated with the length of history of prostatism (χ^2, $P > 0{\cdot}05$), age, serum creatinine and acid phosphatase (Mann–Whitney tests, $P > 0{\cdot}05$) or time of catheter removal (χ^2, $P > 0{\cdot}05$). The mean residual volume of urine in the 'successes' was 750 ml and 1200 ml in the 'failures' (Mann–Whitney test, $P = 0{\cdot}014$).

These seventeen successful patients were reviewed 6 months later. None reported further urinary retention. Six (35·3 per cent) had required prostatectomy for severe symptoms. Six (35·3 per cent) had minor symptoms. Five (29·4 per cent) were symptomless.

We conclude that trial without catheter is worthwhile, since 11 (18·3 per cent) out of 60 patients had not required surgery when reviewed after 6 months. Patients with a low residual volume of urine are most likely to benefit.

Is tumour destruction by laser photodynamic therapy mediated by vascular effects?

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The mechanism of tumour destruction by laser photodynamic therapy (PDT) may be mediated by vascular disruption[1]. We have made quantitative measurements of blood flow during PDT to determine when blood flow effects begin.

Twenty CBH rats bearing a transplantable fibrosarcoma in the flank were investigated. Fifteen animals were photosensitized by injecting 5 mg/kg aluminium sulphonated phthalocyanine intravenously, the remainder acting as controls. The tumours were exposed by skin incision, and light (wavelength 675 nm) from a dye laser directed onto the surface of the tumours at a power of 200 mW. Exposures of 1 min, 3 min or 9 min were given. The tumour blood flow was measured during laser treatment and for 9 min subsequently using a laser doppler flowmeter (Perimed, Sweden).

Table 1 *Blood flow during PDT (percentage of initial flow ± s.d.)*

Treatment	1 min of PDT	3 min of PDT	9 min of PDT
AlSPC	39±13*	24±6	10±1**
Control	96±3*	96±19	96±33**

* $P<0{\cdot}05$, ** $P<0{\cdot}02$ (Student's *t* test)

Table 2 *Blood flow after PDT (percentage of initial flow ± s.d.)*

Treatment	1 min after PDT	3 min after PDT	9 min after PDT
1 min PDT	47±8	49±10	59±11
3 min PDT	29±3	29±2	43±8
9 min PDT	11±1	11±1	16±3
Control	95±39	94±39	87±36

Blood flow decreased rapidly in the sensitized tumours during PDT, and subsequently made a partial recovery. It remained unchanged in the control groups. A marked diminution of blood flow is an early event in tumour death following photodynamic therapy.

1. Henderson BW, Waldow SM, Mang TS, Potter WR. Tumour destruction and kinetics of tumour cell death in two experimental mouse tumours following photodynamic therapy. *Cancer Res* 1985; **45**: 572.

Can 'diced' skin improve expansion in grafting granulating wounds?

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Split skin grafts (SSG) leave unsightly donor sites and for extensive wounds may be meshed for up to four-fold expansion. A technique of slicing 200 μm skin fragments to achieve 20–30 fold expansion has been evaluated.

In anaesthetized pigs, skin and subcutaneous fat were excised from the back to make 60 cm wounds which granulated for 1 week and were then randomized to either (i) meshed grafts prepared from 20 cm² SSG, (ii) 200 μg fragments 'diced' by microtome from 2 cm² SSG and (iii) no graft. Occlusive dressings (Granuflex, Squibb Surgicare) were applied to all wounds and measured weekly by tracing onto card of known area to weight ratio.

	Mean wound area (cm²)			Healing rate (cm²/week)	
	Start	1st week	2nd week	1st week	2nd week
Control (*n*=8)	41·4±1·8	21·4±1·1	20·5±1	19·3±1·1	0·9±0·2
Meshed (*n*=10)	40·7±1·6	6·2±1*	0·74±0·5*	34·5±1*	5·4±0/7*
Diced (*n*=10)	42·3±1·5	8·6±1·4*	*3·3±1	32·1±1·4*	5·3±0·8*

Results mean ± s.e.m. *$P<0{\cdot}001$ compared with control (Mann–Whitney test)

Rapid healing of large wounds was achieved using both meshed and diced SSG. At both 1 and 2 weeks, ulcer size was significantly smaller and healing rate greater with meshed and diced SSG compared with controls. Despite greater expansion of ten-fold the healing rate with diced skin was similar to that of meshed SSGs.

Small skin fragments can achieve healing of granulating wounds with total expansion of more than 20–30 times. This technique provides a simple alternative to skin culture for large wounds and enables wider use of local anaesthesia in smaller wounds and ulcers.

Minilaparoscopy versus peritoneal lavage in blunt abdominal trauma—preliminary results of a controlled clinical trial

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The minilaparoscope was developed to enable inspection of the peritoneal cavity under local anaesthesia without the operating theatre. Following preliminary evaluation in the acute abdomen and blunt abdominal trauma, a prospective randomized study was set up to evaluate the benefits of minilaparoscopy *versus* peritoneal lavage in blunt abdominal trauma.

Patients with abdominal signs and stable haemodynamic state were randomized either to abdominal lavage ($n=26$) or minilaparoscopy ($n=29$). The age range of the 55 patients was 7–68 years (median 26 years). Multiple injuries were present in 49 patients and there were 7 deaths.

1. *Lavage group.* Fifteen patients had negative and eleven patients positive lavage. The latter were subjected to laparotomy. Significant abdominal trauma or active bleeding was found in eight patients.

2. *Minilaparoscopy:* This was negative in 12 patients, showed a minimal static haemoperitoneum in 4, moderate/severe haemoperitoneum in 12 and free intestinal fluid in 1 patient. The patients with moderate to severe haemoperitoneum and free intestinal fluid were subjected to laparotomy ($n=13$) and all but one had significant abdominal trauma or active bleeding.

There was no morbity attributed to either lavage or minilaparoscopy. The negative laparotomy rate was 3/11 for lavage and 1/13 for minilaparoscopy. None of the patients with negative lavage or minilaparoscopy required abdominal surgical intervention.

Drug-induced augmentation of tumour metastasis

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Numerous studies have demonstrated that the cells within a tumour are heterogeneous with regard to several properties including metastatic capability. Heritable changes can be induced in cell populations by environmental agents and drug treatment. Such agents are believed to act by inducing stable changes in gene expression.

The tumorigenicity and metastatic behaviour of a murine mammary tumour line (P574) were studied using two such drugs. 5-aza-2′-deoxycytidine is an analogue of 3-azacytidine, a hypomethylating drug used in the treatment of acute myeloid leukaemia. Tetradecanoylphorbolacetate (TPA) is a known promoter of murine skin tumours but its effect on metastatic behaviour has not previously been studied.

P574 cells were treated *in vitro* with a single dose of either drug (5 μM 5-aza-2′-deoxycytidine, 10 ng/ml TPA) for times varying from 1–24 h. After 24 h recovery, cells were inoculated into the fat pad of syngeneic hosts (C3H-Avy mice). The effects on tumour growth and metastatic behaviour were documented.

	Length of exposure *in vitro*	Pulmonary metastases
5-aza-2′-deoxycytidine	0 h	2/30 animals
	4 h	0/6 animals
	24 h	5/8* animals
TPA	0 h	2/30 animals
	1 h	5/8* animals
	4 h	4/6* animals

* $P>0{\cdot}01$; χ^2 test

Both drugs reduced the latent period of tumorigenicity of P574, and also caused a significant augmentation of metastasis.

As several generations of cell division occur between tumour inoculation and metastasis, this increase in spontaneous metastasis must reflect a heritable change induced by external agents.

Correspondence

Blood transfusion and cancer recurrence

Sir

The suggestion that blood transfusion induces immunological incompetence allowing more aggressive behaviour from some tumours cannot be dismissed lightly (*Br J Surg* 1987; 74: 26–30). Francis and Judson in suggesting that transfusion practice need not change correctly state that there is little hard evidence to support a direct causal relationship between blood transfusion and early recurrence of cancer following surgery[1]. There is however a considerable body of evidence which demonstrates consistently poorer survival and earlier recurrence in cancer patients transfused in the peroperative period.

It is also apparent from several studies that the volumes transfused are rarely in excess of 2 units. Superficially at least it would seem that blood transfusion is not often required for acute haemodynamic disturbance and is more commonly employed expeditiously to achieve a 'satisfactory' haemoglobin value.

We have now had the opportunity to study survival experience in 126 patients having surgery for renal carcinoma[2]. Transfused patients appear to fare worse with uncontrolled comparison ($P < 0.05$, Logrank test). This difference is reduced to non-significant levels when analysis is controlled for such confounding variables as age, stage and presenting haemoglobin.

We would agree with Francis and Judson regarding the value of retrospective studies of this nature. Despite a lack of statistical significance, survival experience remains poorer in transfused patients in our own and other studies. Prospective studies, preferably randomized, are necessary to document blood usage in cancer surgery. Until these are available caution should be exercised in the administration of blood products and the requirements for transfusion should be carefully assessed in each individual case.

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Admission guidelines for head injuries

Sir

I am puzzled by the conclusions reached by the authors of this paper (*Br J Surg* 1986; 73: 891–3). If I understand the figures correctly the position is as shown in *Figure 1*.

Of the original 5850 patients who underwent skull X-ray, 2764 were excluded from further study. I think that these were children and multiply injured adults. Of the remaining 3086 they excluded 55 because of inadequate data. This left 3031 patients for study. 759 fulfilled 'admission criteria' and 2272 did not. Of the 759 who did fulfil admission criteria some 387 were sent home. Of the 2272 without admission criteria some 1954 were sent home. This gives a total of 2341 who were sent home by the various departments. The 690 adults who were admitted were drawn from the two groups. 372 did have admission criteria and 318 did not. I think that the 9 who had some important complication were in the group of 372 who did fulfil admission criteria. We do not know what criteria were used by the various hospitals but the 690 who *were* admitted represented a smaller number than the 759 who *would have been* admitted if admission criteria had been used in each case. Thus 'existing criteria' seemed to be more economical than the guidelines. The potential 46 per cent reduction in admissions that the authors mention could only be achieved if all patients who did not satisfy admission criteria were sent home *together with* the 387 who *did* fulfil admission criteria but were sent home for reasons which are not stated. It seems as though they are advocating a combination of 'admission criteria' as well as 'existing criteria' in order to achieve this rather large potential reduction in workload.

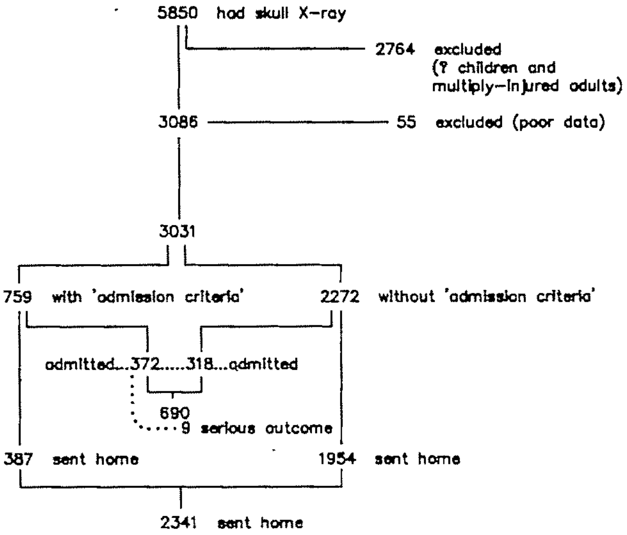
5850 had skull X-ray
2764 excluded
(? children and multiply-injured adults)
3086
55 excluded (poor data)
3031
759 with 'admission criteria'
2272 without 'admission criteria'
admitted...372.....318...admitted
690
9 serious outcome
387 sent home
1954 sent home
2341 sent home

Figure 1 *Admission guidelines for head injuries*

My immediate impression is that this would cause more difficulties for accident departments than benefits. Medicolegally it would now be very difficult to defend the decisions to send home someone who does fulfil admission criteria, even though he/she might have been sent home in the past and even though this is the only way to achieve the reductions in workload and expenses suggested by the authors.

R. J. Cherry

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UK

Authors' reply

Sir

The interpretation by Mr Cherry of the data in our paper is quite correct. We agree that medicolegally it would be more difficult to defend the decision to discharge a patient with admission criteria. But this should not prevent implementation of the guidelines. If 100 per cent compliance is achieved, admissions would increase by 10 per cent, but 23 per cent of patients would have more appropriate care as described in the guidelines. We are not advocating that patients with admission criteria should be discharged, but did point out in the paper that previous experience with the implementation of other guidelines suggests that many such patients might well continue to be discharged, leading to an overall reduction in admissions.

Doctors who are worried about the medicolegal consequences may be tacitly expressing some concern about the appropriateness of the guidelines and their ability to comply with them. Under these circumstances they would be advised to await the results of studies in which the guidelines are being implemented experimentally as part of the evaluation of comprehensive guidelines for the management of head injuries.

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Book reviews

Diagnostic Techniques and Assessment Procedures in Vascular Surgery

R. M. Greenhalgh. 260 × 180 mm. Pp. 505 + xvi. Illustrated. 1986. London: Grune and Stratton. £57.50.

The yearly vascular symposium arranged by Professor Greenhalgh has become established on the vascular surgery calendar. The resulting book is written by the many leading surgeons who attend and some devoted more time to writing their chapters than others. The 1985 symposium covered diagnostic techniques at a time when there has been an explosion in the methods available. One of the major aims of the book is to assess the value of this galaxy of research tools to the practising clinicians who have limitation of time and resources.

The book is well laid out in sections and it is surprisingly comprehensive considering that no symposium can cover all the topics. The text is well edited, readable and supported by high quality illustrations. The inevitable criticism of any book written by enthusiasts for a technique is that the reader can remain uncertain about the drawbacks and problems. It is therefore refreshing to read the chapter by David Charlesworth on 'Hydraulic Impedence' explaining why this ideal measurement remains unobtainable.

Some of the chapters give useful practical advice (e.g. 'Assessment of the Deep Venous System' by David Negus) and others are thought-provoking for future developments (e.g. the two chapters on 'The Measurement of Peripheral Resistance'). Overall this book is enjoyable to browse through and contains much useful information. The price of textbooks has risen enormously and £57.50 for 500 pages is a little daunting.

J. H. N. Wolfe

Renal and Urologic Emergencies

A. B. Wolfson and A. Harwood-Nuss. 240 × 165 mm. Pp. 291 + xi. Illustrated. 1986. Edinburgh: Churchill Livingstone. £28.00.

This book is not, as the title would suggest, a guide to urological emergencies, but one of a series of *Clinics in Emergency Medicine* from North America directed at the emergency department and the primary care physician. No one would be surprised to find priapism discussed but to have included Peyronie's Disease, with its slow and insidious nature, suggests undue editorial laxity. In addition to the two editors there are 22 contributors for 13 chapters. Much of the subject matter is considered in considerable depth and with extensive references—an average of 51 per chapter. There is plenty of excellent material which the trainee in surgery or accident and emergency medicine would find of interest, but it is not a handbook for the casualty officer looking for practical guidance. There are few illustrations, but two practical procedures which are illustrated, passing a catheter on an introducer and negotiating a stricture with filiform bougies, have little place in modern endoscopic urology and certainly none in the accident and emergency department.

For all its scholarly approach and excellence, one feels this is a book from 'over there' which will do rather less well 'over here'.

N. W. Harrison

Cancer and its Management

R. Souhami and J. Tobias. 250 × 190 mm. Pp. 526 + viii. Illustrated. Oxford: Blackwell Scientific Publications. £55.00.

Oncology is one of the most rapidly expanding of all medical specialties and one which demands co-operation and integration of a large number of clinicians. This book describes state of the art diagnosis and management of the full gamut of malignancies, system by system, in a clear, concise and readable manner which stresses the multidisciplinary approach. Each chapter is only 15–25 pages long and is complemented by compact tables, precise schematic line drawings and between 10 and 30 key references. It is particularly refreshing to see that equal space has been devoted to rare tumours such as soft tissue sarcoma as has to common malignancies such as breast cancer.

Although the book is primarily targeted towards medical students (both undergraduate and postgraduate) and general practitioners for whom it provides an up-to-date overview, it would be a valuable addition to the libraries of surgical and oncological departments. The price is its main drawback, for I doubt that many students will justify spending £55 unless a cheaper softback edition is planned.

M. W. Kissin

Electrosurgery

J. A. Pearce. 240 × 160 mm. Pp. 258 + x. Illustrated. 1986. London: Chapman and Hall, £35.00.

Whilst the majority of surgeons use high-frequency currents for cutting and coagulation on a daily basis, very few of us understand the basic principles of electric field theory on which electrosurgery is based. This monograph, by a biomedical engineer at the University of Texas, deals with the engineering aspects and, although clinical applications are cited, it goes well beyond the knowledge required by most surgeons. I am not quite sure for whom it is written. Medical physics departments would find it a useful introductory book but the only readers in the operating theatre might be some of the technical staff or tutors.

Chapters include historical background, electrosurgical generators, and cutting and coagulation processes. It is quite worrying to read what goes on under the dispersive electrode and prepares you for an important chapter on hazards. Recommendations to avoid complications are clearly stated in the text but could have been itemized in the summary.

R. McCloy

Advances in Wound Management

T. D. Turner, R. J. Schmidt and K. G. Harding. 230 × 150 mm. Pp. 149 + vii. Illustrated. 1986. Chichester: John Wiley and Sons. £11.95.

An accurate account of a conference held in March 1985 is given in which initiators of new wound management products could declare in a seminar the nature, usage and advantages of their materials. These products are placed in recognizable groups and preceded by overview papers which give the general chemical, physical and performance characteristics of each group.

The overview sections are relevant, concise and interesting and give an up-to-date account of the position and characteristics of the various groups of dressings. The accounts of the experimental methods which might be used to determine the physical and chemical properties of the dressings could have been explained in greater detail.

The sections in each dressing group for the various companies varied in quality. Some are excellent giving much clinical detail in trial and control trial situations with an attempt at costing of dressings in hospital and the community. Other dressings are very scantily presented with anecdotal descriptions in a few patients. There is a discussion section at the end of each group of presentations and these do help to form a basis for the many unanswered problems about types of dressings and what should be used in various situations. Many of these questions remained unanswered, but stimulation to the problems in hand is certainly emphasized.

The book is soft backed, easily read and accurately texted with, in general, relevant black and white photographs. Some of these are not too well produced. Each of the chapters has a relevant reference section. The sparsity of references in some represents the lack of scientific data on some of these products. The book is an up-to-date reference for the state of the art in wound dressing management, at a price of £11.95.

R. A. B. Wood

Surgery of the Stomach and Duodenum. Fourth edition

L. M. Nyhus and C. Wastell. 260 × 190 mm. Pp. 914 + xvii. Illustrated. Edinburgh: Churchill Livingstone. £89.00.

In the foreword to this book it is stated that, despite the major changes which have taken place in gastroenterology, the need for a book on surgery of the stomach and duodenum is greater than before. I would agree with this statement, for today surgeons are, during their training, gaining far less experience in gastric surgery than several years ago but the need for gastric surgery and gastric surgical refinements remains and the techniques involved, particularly in the treatment of gastric malignancies, are becoming more advanced and sophisticated.

Once again this book begins with an extensive and fascinating historical review of the subject. There is a crisp and easily read chapter on gastric physiology. The section on diagnostic techniques is helpful and appropriate to the present diminishing role of gastric secretion tests and the increased importance of upper gastrointestinal endoscopy. A completely new chapter entitled 'Duodenal Reflux Syndrome', whilst purporting to describe something new, only contains two references more recent than 1981 and makes no mention of the role of cholecystectomy in exacerbating this problem. The chapters on gastric ulcer contain valuable advice and make most useful reading. In a special comment at the beginning of the section on duodenal ulcer Oi gives a reappraisal of sub-total gastrectomy for duodenal ulcer which did not appear in previous editions of this book and I feel that few Western surgeons would nowadays employ this technique. Chapters follow, however, on truncal and selective vagotomy, the latter technique being beautifully illustrated and described prior to a description of proximal gastric vagotomy. The first of these chapters has been completely re-written and the latter two extensively updated; they provide a detailed, accurate overview of these procedures. A special comment on proximal gastric vagotomy by Holle emphasizes, in his view, the importance of adding a drainage procedure to proximal gastric vagotomy, stating that this compensates for the disadvantages of proximal gastric vagotomy alone. The question of whether or not to combine a drainage procedure with proximal gastric vagotomy remains unresolved, but Holle's results are impressive in a massive series of 1405 patients. The rate of recurrent ulceration is a strikingly low, 2·7 per cent for duodenal ulcer over a 5–16 year period with an increase of dumping of 4·5 per cent, which may be justified in view of the low rate of recurrence. The editor emphasizes the importance of the problem of recurrence after proximal gastric vagotomy; he cautions the reader recommending its selective use but does not state how selection should be made. In addition, he does not recommend that pyloroplasty should be added to the procedure. The strong trans-Atlantic flavour in this book is again apparent from Sawyers and Herrington's chapter on vagotomy and antrectomy which is clearly regarded by the editor as the 'gold standard' against which other procedures must be compared. At the same time, however, the point is made that this form of surgery permanently removes the ulcer diathesis in 99 per cent of patients, whereas the prolonged use of H_2 receptor antagonists, which receive remarkably scant attention herein, never permanently cure this disease.

In keeping with the changing attitudes of the day the chapter on Billroth II gastrectomy has been completely removed from the present edition. The chapter on Zollinger–Ellison syndrome has been completely re-written by its eponymous founder with emphasis on the increasing role of H_2-receptor antagonists; regardless of this, however, it is recommended that every patient should undergo surgical exploration and the value of peroperative ultrasound is stressed. An excellent chapter on gastro-oesophageal reflux is included and a new and very important chapter by Mason has been added on gastric reduction for morbid obesity. The latter is becoming one of the largest fields of gastric surgery.

With such a formidable array of contributors few could doubt or argue with the fact that this book remains the bible for those dedicated to surgery of the stomach and duodenum. It remains as valuable as a reference book as it does an authoritative, interesting and readable textbook. Its broad based, all embracing and often historical commentary give both the established gastric surgeon and the surgical trainee a depth of insight and experience which in these changing times will be elusive and probably will never be attained again.

T. V. Taylor

Major Ambulatory Surgery

J. E. Davis. 260 × 180 mm. Pp. 494 + xiii. Illustrated. 1986. London: Williams and Wilkins. £66.

Ambulatory surgery is translated into English as 'Day Case Surgery'. The concept is not new, indeed before the Victorian economic miracle and consequent hospital building few patients who were not indigent entered hospital for surgery. Hospital was too expensive in terms of sepsis and delayed recovery. Today hospital is too expensive in terms of pounds and pence in the UK or in dollars in the USA. Ambulatory surgery is therefore having a vigorous revival.

This book is an excellent review of American experience; of particular interest are the organizational, economic and architectural chapters. Many problems with day case surgery in the UK stem from organizational failure, a point well made in this account of the transatlantic experience. Not only have we organizational failure but also a curious reluctance by British hospital architects to get a good design together; this book will tell them how to do it. Commitment is another shortfall in the NHS. American surgeons have strong economic commitment to do more better quality surgery than their competitors and the good old market forces have predicated the expansion of ambulatory surgery—could we not learn from this?

I've enjoyed this vigorous book and recommend British surgeons, nurses and administrators to learn from it. After all 40 per cent of surgery in all disciplines in the NHS could readily be done on an ambulatory basis and that would make an enormous difference to the NHS budget.

H. B. Devlin

Essentials of Clinical Anatomy

R. Ger and P. Abrahams. 245 × 185 mm. Pp. 530. Illustrated. 1986. Harlow: Longman Group. £24.95.

This book is aimed at medical students. It reads well and is attractively presented, starting with an excellent vocabulary and ending with interesting historical notes on famous names in anatomy. Each section ends with multiple choice questions to help the student to revise.

The book is written in colloquial style which is intended to hold the student's attention. Part of the text is taken verbatim from lectures delivered to preclinical students. However, some of the colloquialisms are better said in a lecture theatre than written in a scientific textbook. It would be better to avoid terms such as 'a sick Meckel's diverticulum'.

The accent is on function and clinical application rather than detailed anatomy. Some of the statements made are debatable. For example, the stomach is described as the largest part of the gastro-intestinal tract. The section on the hand and its function is detailed and clear. The section on the portal circulation, however, omits to mention some named tributaries. Surface anatomy is well described throughout.

The text is illustrated by good radiology including arteriograms and venograms, cholangiograms, CT scans and ultrasounds. There are frequent diagrams which are often oversimplified as in 29.3 which omits to show the cystic artery in a diagram of the structures in the free edge of the lesser omentum and in some cases they are inaccurate. Diagram 32.3 shows the piriformis muscle on the dorsum of the sacrum, and 29.3 shows the superior and inferior mesenteric arteries arising from a common origin from the aorta.

The book requires some revision particularly of the diagrams but when this has been carried out it will be a helpful and readable book for medical students studying anatomy for their first degrees.

D. Reid

Plastic Reconstruction in the Head and Neck

T. R. Bull and E. N. Myers. 234 × 165 mm. Illustrated. London: Butterworths. £40.00.

It is reasonable to expect the title of a book to give some indication of its contents. Most readers would open this book expecting to find detailed accounts of reconstructive surgery of the mouth, neck and face, and indeed the first two chapters are on oral cavity reconstruction and reconstruction of the hypopharynx and cervical oesophagus. Apart from an excellent final chapter on eyelid reconstruction, however, the rest of the book is a mixture of pure ear, nose and throat surgery and aesthetic surgery, including 45 pages (one-fifth of the book) on management of the balding scalp. The authors are mostly from ear, nose and throat departments in Europe and America and there is not one contributor from the field of plastic and reconstructive surgery.

When viewed in their own context many of the contributions are excellent. The first chapter on oral cavity reconstruction places some emphasis on prosthetic work, but the only reconstructive options described are free grafts and pectoralis major myocutaneous flaps. Although the advantages of one-stage repairs are emphasized, central mandibular defects are treated by soft tissue repair followed by staged bone grafts, and there is no mention of osteocutaneous flaps or other free flaps in oral cavity reconstruction. The second chapter on reconstruction of the pharynx and cervical oesophagus is well written, but does not always quote personal experience, and there is no mention of the use of the radial forearm flap. One's confidence in the author's reconstructive understanding is slightly shaken by the error in Figure 2.1 which shows a deltopectoral flap being used for pharyngeal reconstruction, with the flap tubed with the skin on the outside! Chapter 3 on voice and airway rehabilitation and six on nasal fractures are excellent and detailed, but chapter four on petrosectomy and facial nerve reconstruction has little description of reconstructive techniques and makes no mention of the need for training in reconstructive microsurgery in order to carry out nerve grafting. Chapter 5 on cosmetic rhinoplasty is disappointing, being vague and discursive, and there is no detailed technical description. Chapter 8 on nasal implants is extremely well written and gives a useful review of the available techniques. It would be helpful if details of the collection and storage of cartilage allografts were included.

There are some worthwhile contributions to this book. It is a pity that it does not fit its descriptive title.

D. M. Evans

Notices and announcements

Meetings

22–26 June 1987
Peritoneum and Peritoneal Access
Lund, Sweden
Information: Professor S. Bengmark, Professor of Surgery, Box 5121, S-220 05 Lund 5, Sweden

24–28 June 1987
Annual Meeting of the Western Thoracic Surgical Association
Colorado Springs, USA
Information: Western Thoracic Surgical Association, 13 Elm Street, Manchester, MA 01944, USA

6–11 July 1987
11th Congress of the International Society on Thrombosis and Hemostasis
Brussels, Belgium
Information: Professor Marc Verstraete, Katholicke University of Leuven, Department of Medical Research, Campus Gasthuisberg, 3000 Leuven, Belgium

7–8 July 1987
Blood Flow '87 (Biological Engineering Society – Blood Flow Group)
University of Leeds, UK
Information: Mr R. Price, Department of Medical Physics, Leeds General Infirmary, Leeds LS1 3EX, UK

9–10 July 1987
Surgical Research Society Meeting
Leeds, UK
Information: Professor I. Taylor, Surgical Research Society, University Surgical Unit, F Level, Centre Block, Southampton General Hospital, Tremona Road, Southampton, UK

9–11 July 1987
XIIth International Update on Liver Disease
London, UK
Information: Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

11–12 July 1987
Summer 1987 Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, c/o Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

19–24 July 1987
Mechanisms of Carcinogenesis
Saxtons River, Vermont, USA
Information: Robert W. Krauss, Executive Director, FASEB, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

26–31 July 1987
Biology of Tumor Metastases
Saxtons River, Vermont, USA
Information: Robert W. Krauss, Executive Director, FASEB, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

9–14 August 1987
Energy Regulation of Energy Balance
Saxtons River, Vermont, USA
Information: Robert W. Krauss, Executive Director, FASEB, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

24–28 August 1987
The Prevention and Management of Organ Failure
London, UK
Information: The Conference Organizer, Critical Care '87, BJHM, Battersea Business Centre, 103–109 Lavender Hill, London SW11 5QL, UK

31 August–4 September 1987
Surgical Efficiency and Economy
Lund, Sweden
Information: Professor S. Bengmark–SEE, Box 5121, S-220 05 Lund 5, Sweden

6–8 September 1987
An Introduction to Laser Surgery
Sheffield, UK
Information: Mrs V. M. Coomer, Regional Conference Centre, Lodge Moor Hospital, Sheffield S10 4LH, UK

9–11 September 1987
Clinical Controversies in Inflammatory Bowel Diseases
Bologna, Italy
Information: Organizing Secretariat, SO.GE.PA.CO. Spa. piazza Constituzione, 5/c, 40128, Bologna, Italy

15–18 September 1987
The British Society of Gastroenterology Jubilee Meeting
London, UK
Information: The Administrative Secretary, The British Society of Gastroenterology, 3 St Andrew's Place, Regent's Park, London NW1 4LB, UK

18–22 September 1987
69th Annual Meeting of the American Association of Oral and Maxillofacial Surgeons
San Francisco, California, USA
Information: K. H. Hajduk, 211 East Chicago Avenue, Suite 930, Chicago, Illinois 60611, USA

9–14 October 1988
The Australian Cranio-Maxillo-Facial Foundation International Workshop on Cranio-Facial Trauma
Adelaide, South Australia
Information: Mrs D. Moody, Executive Officer, 226 Melbourne Street, North Adelaide S A 5006, Australia

11–16 October 1987
Annual Clinical Congress of the American College of Surgeons
San Francisco, California, USA
Information: American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

15–17 October 1987
Fourth Meeting of the European Chapter of the International Union of Angiology
Brussels, Belgium
Information: Madame D. Shanni, Administrative Secretariat, ECCO, Rue Vilain XIIII, 17a, B-1050 Brussels, Belgium

18–24 October 1987
Recent Advances in Pancreaticobiliary Surgery
Glasgow, UK
Information: Professor D. C. Carter, University Department of Surgery, Queen Elizabeth Building, Royal Infirmary, Glasgow G31 2ER, UK

22–23 October 1987
First British Symposium on Surgical Stapling
Manchester, UK
Information: Conference Coordinates, Confer House, 69 Kingston Road, New Malden, Surrey KT3 3PB

24–25 October 1987
Autumn '87 Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, c/o Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

30 October–3 November 1987
8th Asian Congress of Thoracic and Cardiovascular Surgery
Singapore
Information: Dr N. C. Tan, Academy of Medicine, Singapore, 4-A College Road, Singapore 0316

Notices

Volunteers needed for 3–6 weeks surgical appointments in overseas Mission Hospitals. Please contact: Mr M. W. Flowers, Accident and Emergency, General Infirmary, Great George Street, Leeds LS1 3EX.

Leading article

Br. J. Surg. 1987, Vol. 74, July, 553–554

Bowel preparation for colorectal surgery

This issue of the Journal contains a paper by Irving and Scrimgeour which challenges accepted surgical practice (pages 580–581). It is a veritable little bomb of a paper, brief, iconoclastic, and disrespectful of hallowed tradition in colorectal surgery. The authors argue that pre-operative bowel preparation is time-consuming and expensive, unpleasant to the patient — even dangerous on occasions — and completely unnecessary. They point out, correctly, that it is impossible to sterilize the bowel, and that the solid contents of unprepared bowel are easier to deal with at operation than the liquid contents of ill-prepared bowel. Provided that a single dose of 'appropriate' antibiotics (cefuroxime and metronidazole) is administered intravenously at the start of the operation, they claim that pre-operative bowel preparation both by mechanical methods and by the use of oral antibiotics may be omitted.

Their comments on bowel preparation aside, it is all stirring stuff, terse and decisive: 'drains and colostomies were never used' and 'free oral fluids were encouraged within the first 24 h'.

The results obtained in a consecutive series of 72 patients who underwent colonic resection with anastomosis were certainly impressive: operative mortality was 3 per cent, the two deaths being from myocardial infarction and cerebrovascular accident, there was no clinically evident anastomotic dehiscence and the incidence of wound infection was 8 per cent. To surpass these figures would be very difficult, and to do so to a statistically significant degree virtually impossible. Most authors who have used more conventional methods of mechanical bowel preparation, combined with the use of antibiotics in various ways, quote incidences of wound infection ranging from 5 to 20 per cent, though it should be noted that Matheson's group[1] in Aberdeen found incidences of wound infection of only 1·8 per cent among 167 consecutive patients who underwent elective colorectal surgery, and of 6·7 per cent after 60 emergency procedures, for an overall incidence of wound infection of 3 per cent. In our own Department over the past 10 years, we have routinely employed a regimen of pre-operative mechanical bowel preparation, combined with the use of three 'shots' of gentamicin and metronidazole intra- and postoperatively, yet our monthly audit continues to show a median incidence of wound infection during the patient's stay in hospital of over 10 per cent.

Are they right or are they wrong? Whatever 'common sense' might dictate, we certainly cannot say that they are wrong because, not only are their results impressive, no-one has used their methods, with the addition of bowel preparation, and obtained better results. Though Rosenberg *et al.*[2] noted a higher incidence of septic complications in patients whose bowel was seen to be loaded with faeces at operation, Hughes[3] contended that pre-operative bowel preparation made little difference to the outcome of colorectal surgery. While spillage of faeces into the peritoneal cavity at operation is obviously undesirable, and such spillage is more likely to occur if the colon is full of faeces than if it is empty, it does not necessarily follow, as an argument based on first principles might seem to dictate, that a vigorous attempt to achieve an empty colon is in the patient's best interests. There are several reasons for this. First, the bowel preparation is often irksome to the patient, preventing the rest and sleep that is so important before a major operation. Secondly, no method of bowel preparation can be relied upon to achieve a 'dry', empty colon in all cases, especially in the presence of large or constricting growths. Thirdly, the use of osmotically active purgatives and large amounts of fluid may lead to fluid overload and congestive cardiac failure in elderly patients. Fourthly, some agents such as mannitol may actually encourage bacterial proliferation[4], with several days' sojourn in hospital before operation may permit colonization of the intestinal tract by dangerous ward organisms, and also predispose to the development of deep venous thrombosis. Thus proof is lacking that patients benefit, overall, from vigorous pre-operative bowel preparation.

Thus, we should be open-minded about this paper, and respect both its originality and the results achieved. However, some serious reservations must be expressed. First, the numbers of patients studied were relatively small, and nine emergency cases were

0007–1323/87/070553–02$3.00

excluded from the series because the performance of an anastomosis was felt to be contra-indicated in the presence of peritonitis. Since pre-operative mechanical bowel preparation is in any case impossible in emergency cases, we are left to focus, not on 72 cases, but on the consecutive series of 53 elective cases. These 53 cases then have to be subdivided into four quite small sub-groups, the most interesting and crucial of which, the patients having low anterior resection, is also the smallest, containing only seven patients. Low anterior resection represents the sternest challenge in this type of surgery, as it tends to be associated with the highest incidence of anastomotic leakage, both overt and occult. Thus one would tend to judge the potential value of a new method more by how patients fare after low anterior resection than after, say, right hemicolectomy, in which control of the bowel ends and bowel content is much easier to achieve. Not only were there only seven elective low anterior resections, but we are told nothing about the size, fixity or height of the tumours above the anal margin, or even about the age or sex of any of the patients. We are also not told whether any mechanical or cytotoxic cleansing of the anorectal stump was carried out during the operation.

While mechanical bowel preparation was omitted, and good results were obtained, it is by no means self-evident that the omission of bowel preparation led to the good results, or even made an important contribution to them. Perhaps the authors would have achieved as good or slightly better results if mechanical bowel preparation had been used. The achievement of excellent clinical results in colorectal surgery stems from a whole package of measures (as Matheson's group has emphasized[1]), which includes the precise method by which the anastomosis is made, the use of antibiotics — type, dose, route of administration, duration — peritoneal lavage, swabbing the edges of transected bowel, the type of incision, and the use or non-use of drains and of defunctioning stomas. All these are important variables that could influence the outcome. Last but not least is the skill of the surgeon, which as Fielding's group[5] showed is of literally vital importance in determining the outcome. What part any or all of these variables played in Irving and Scrimgeour's achievement is impossible to tell. However, Irving's close association with the Aberdeen work in the past is duly noted[10]. My hunch would be that shrewd selection of cases and of operative method in the emergency group, the use of an inverting, one-layer anastomosis[6], peritoneal lavage[1,7] and the absence of drains may have contributed more to the good results obtained than the omission of bowel preparation. Indeed it is conceivable that these factors might have compensated for the omission of bowel preparation. No-one can be sure, until the appropriate prospective trial is done to isolate mechanical bowel preparation as a single variable that can be evaluated in a scientific manner.

D. Johnston

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1. Krukowski ZH, Stewart PMP, Alsayer HM, Matheson NA. Infection after abdominal surgery: 5 year prospective study. *Br Med J* 1984; **288**: 1, 278–80.
2. Rosenberg IL, Graham NG, DeDombal FT, Goligher JC. Preparation of the intestine in patients undergoing major large bowel surgery mainly for neoplasm of the colon and rectum. *Br J Surg* 1971; **58**: 266–9.
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4. Keighley MRB, Taylor EW, Hares MM *et al.* Influences of oral mannitol bowel preparation on colonic microflora and the risk of explosion during endoscopic diathermy. *Br J Surg* 1981; **68**: 554–8.
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6. Matheson NA, Irving AD. Single layer anastomosis after rectosigmoid resection. *Br J Surg* 1975; **62**: 239–42.
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Br. J. Surg. 1987, Vol. 74, July, 555–560

Appraisal of the management of bile duct stones

A. G. Johnson and S. W. Hosking

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Professor A. G. Johnson

This review discusses the natural history, diagnosis and treatment of stones in the bile ducts. A rational plan of management is outlined.

Keywords: Gallstone, bile duct, dissolution, extraction

Choledocholithiasis is a condition that general surgeons face numerous times during their surgical careers. Typically they will encounter it during cholecystectomy and, traditionally, will remove the offending stones with Desjardin's forceps, a Fogarty catheter, by flushing or by other procedures. They may perform choledochoscopy to check whether all the stones have been removed and will almost certainly place a T tube in the common bile duct. Seven to ten days later, a T tube cholangiogram will be performed and provided no stones remain, the T tube will be removed and the patient discharged from hospital. If all goes according to plan the mortality in a fit patient is less than 1 per cent[1]. If stones remain, or if the problem is complicated by jaundice, cholangitis, bile duct stricture, previous biliary surgery or medical infirmity, the mortality rises considerably[1] and can reach 12 per cent in young patients[2] and 20 per cent in older patients[3]. During the last 10–15 years there have been a number of advances in the management of the patient with choledocholithiasis with the overall aim of reducing the complications and mortality associated with this condition. Before discussing these advances, it is important to review what is known of choledocholithiasis because this must be the basis of any management.

The natural history of choledocholithiasis

The following facts have been established:

Most common bile duct (CBD) stones migrate from the gallbladder

Several observations seem to support this. First, CBD stones are present in approximately 12 per cent of patients with gallbladder stones at the time of cholecystectomy[4,5], and they usually resemble gallbladder stones in type and morphology[6]; CBD stones are uncommon in the absence of gallbladder stones[6].

Primary duct stones do occur

It is well documented that, in patients with agenesis of the gallbladder, CBD stones may be found. In Gerwig's literature review, of 47 patients with gallbladder agenesis who had biliary symptoms, 43 per cent had CBD stones[7]. Primary duct stones also form in cholecystectomized animals who have a CBD stricture[8] and this association is well recognized in man. It would appear that inadequate biliary drainage is usually the underlying problem. Primary duct stones have a different form and composition, often being soft and friable or consisting of a mudlike mixture[6].

CBD stones may be asymptomatic

In a large autopsy of 1000 patients, Crump found that 24 per cent of patients with cholelithiasis also had stones in the biliary ducts and this proportion was independent of age[9]. Crump also noted that the prevalence of gallstones increased with age and so the number of patients with CBD stones will also increase with age. Similar results were obtained in Lieber's autopsy series[10]. In an operative series where gallstones were presumably symptomatic[11], the prevalence of choledocholithiasis was 6 per cent in younger patients but rose to 33 per cent in those over 80 years. Combining the above data suggests that not only are CBD stones more common in the elderly but a far greater proportion are symptomatic.

Most patients known to have CBD stones will have them removed, but what happens if such patients have no treatment? Millbourn[12] reported on 38 patients before the days of antibiotics who either refused surgery or were considered surgically unfit. In the follow-up period of 6 months to 13 years, 17 (45 per cent) patients had no further symptoms while the remaining 21 (55 per cent) developed complications such as biliary colic, jaundice and cholangitis. In another series[13], 781 patients diagnosed as having gallbladder stones and having no complications or treatment in the year following diagnosis were followed for a further 10 years. During this period, 59 (7·5 per cent) patients developed direct complications of CBD stones such as pancreatitis or jaundice. Within the same group of 781 patients, 27 per cent of those who had a cholecystectomy because of symptomatic gallstones had CBD stones. If 27 per cent of the entire group had CBD stones (which is similar to Crump's figure of 24 per cent), and only 7·5 per cent developed direct complications, this suggests that one-quarter of patients with CBD stones developed serious complications. If a more conservative estimate of 15 per cent having CBD stones is used, then the figure rises to one half.

What is the outcome in patients who have CBD stones left at the time of operation? In the only study of its kind[14], symptoms attributable to duct stones were most pronounced during the first year and also 3 years after CBD exploration. After examining the stones removed at operation, 90 per cent were thought to have originated from the gallbladder and only 10 per cent to be primary duct stones. Because 26 per cent of their patients presented 10 or more years after their initial cholecystectomy, the authors suggest that the onset of symptoms many years after surgery is more likely to be due to enlargement of residual CBD stones than to formation of primary CBD stones.

Bile duct stones may pass spontaneously

In two separate studies, gallstones were found in the faeces of a high proportion of patients with pancreatitis[15,16], but 12 per cent of control patients also had gallstones which ranged from 1 to 12 mm in diameter in their faeces.

In summary, CBD stones usually come from the gallbladder although primary CBD stones do form. Small calculi probably leave the CBD and enter the duodenum without causing symptoms but others remain and will eventually cause symptoms in 25–50 per cent of patients either by their presence in the CBD or as they pass through the ampulla. Although the

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prevalence of gallstones increases with age, the proportion who have CBD stones remains constant. However, as CBD stones are more likely to cause symptoms in older patients, CBD stones are more likely in older patients undergoing cholecystectomy.

Diagnosis

Can CBD stones be predicted pre-operatively?

Several studies have attempted to evaluate whether choledocholithiasis is present on the basis of symptoms, blood biochemistry and ultrasound. This was important before the widespread availability of peroperative cholangiography, but is probably of less value now. The clinical symptoms of abdominal pain, rigors and jaundice almost always indicate the presence of CBD stones but the vast majority of patients with CBD stones do not have Charcot's triad[17]. Lacain *et al.*[18] studied symptoms, blood biochemistry and CBD diameter and calculated a prediction value for each parameter. In their experience of patients not obviously jaundiced, a CBD greater than 12 mm in diameter plus either a raised alkaline phosphatase, minimally raised bilirubin or history of jaundice gave a 90–100 per cent predictive value of CBD stones. It is important to note that a dilated CBD alone (>12 mm diameter) was an unreliable indicator of CBD stones. This may be understood in the light of Lygidakis' experience[19] who found that in addition to stones, CBD dilatation depended on age, previous biliary surgery, biliary infection and a long history. He found CBD stones in 93 per cent of patients with a CBD diameter >15 mm, but 6 per cent of patients with CBD stones had a normal diameter duct. The ability of the CBD to change diameter within a week[20] undoubtedly confuses the issue as does the definition of CBD dilatation when the normal diameter can be as little as 6 mm[21].

While the ability to measure duct diameter by ultrasound is excellent, the same technique was only able to detect CBD stones in 15 per cent of patients subsequently found to have CBD stones[21]. In jaundiced patients, this figure rises to 33 per cent[22] but is still too low to make ultrasound of real value in the correct prediction of CBD stones. Experience with CT scanning indicates that it is also accurate in diagnosing biliary dilatation but like ultrasound is rather less successful in demonstrating CBD stones[23].

In non-jaundiced patients, pre-operative duct visualization with endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) is not performed routinely as both techniques are invasive with a morbidity of 2 per cent and 5 per cent respectively[24,25], and stones can be identified by peroperative cholangiography. Their main use is in the patient with obstructive jaundice to establish the cause and site of obstruction. There is some evidence that ERCP or PTC can be avoided even in jaundiced patients, as a good quality ultrasound examination showing a dilated CBD and small gallbladder containing stones is probably sufficient to diagnose calculous CBD obstruction[26]. However, when ultrasound does not show these 'typical' features for any reason, ERCP or PTC becomes necessary. The temptation to perform endoscopic sphincterotomy at the same time as ERCP, in a patient who is otherwise fit and for whom surgery is planned, should be avoided. Not only does the procedure increase the risk to the patient (see below) but peroperative cholangiography is made very difficult due to air in the CBD and inability to fill the CBD with contrast.

Diagnosing CBD stones at operation

We have already seen that duct dilatation alone is an unreliable indicator of CBD stones and palpation of the duct will often miss small stones as well as intrahepatic stones. Most surgeons perform cholangiography routinely as part of cholecystectomy. Routine use of this technique reduces the number of retained stones[27–29] and also decreases the number of negative CBD explorations[30,31]. The cholangiographic criteria for exploration of the CBD vary from centre to centre but there is considerable evidence that over-exploration rather than under-exploration takes place.

Most series report that 25 per cent of patients undergoing cholecystectomy will have surgical exploration of the CBD but stones are found in only 60 per cent of these patients[4,27,30]. The incidence of retained stones in those undergoing CBD exploration varies between 1 per cent and 10 per cent with an average of 4·3 per cent[32] and this usually occurs in patients in whom some CBD stones are removed[27]. At present there is little evidence to define which criteria other than palpable stones, obstructive jaundice, or a filling defect on cholangiography should be used as indication to explore the CBD. In our own unit we have performed 354 cholangiograms in the last 5 years and explored 84 CBDs. The criteria for exploration were filling defects (76 patients), dilated CBD without filling defect (6 patients) and no duodenal flow (2 patients). There were 8 false filling defects and no stones were found in patients who did not have a filling defect. Four patients (5 per cent) of those who underwent CBD exploration had retained stones; all of them had had choledochotomy with removal of stones.

Although most units perform peroperative cholangiography routinely, it has been suggested that cholangiography in selected patients (based on clinical, biochemical and operative criteria) reduces the number of unnecessary choledochotomies from false positive cholangiograms as well as reducing time and costs[33]. However, no prospective study of selective cholangiography has been reported to date. The key question at present is whether a false positive exploration of the CBD is harmful, and this is considered in the next section.

An alternative to cholangiography is operative ultrasonography. In a comparative study[34], overall accuracy with either technique was similar except that ultrasound was more likely than cholangiography to predict CBD stones correctly. Problems of ultrasonography are mainly operator dependent, but only a few centres are likely to have this option in the operating theatre at present.

Is negative exploration of the CBD harmful?

This is an important question which affects the surgeon's decision at operation. Most studies show that the mortality is greater in patients who have had their duct explored than in those who merely have a cholecystectomy[29,30,32], but this is misleading because the mortality is that of the patient in poor general condition having a major operation and not the extra procedure of duct exploration. Those who require exploration are on average older and are more ill with jaundice, sepsis, and associated cardiovascular and pulmonary disease[3]. McSherry and Glenn[1] have carefully analysed the causes of death after biliary surgery for benign disease and found no evidence that negative exploration is harmful in younger, relatively fit patients. There was one death out of 221 negative explorations which is exactly the same as the mortality for cholecystectomy alone for even acalculous disease. Even with the current experience of endoscopic sphincterotomy, it is better to err on the side of over-exploration rather than under-exploration unless the patient's condition is poor, although these patients may have had endoscopic sphincterotomy beforehand (see below). If in doubt, and if the patient has had a previous gastric resection, it is imperative to explore the duct as the endoscopic approach to the ampulla is extremely difficult[35].

Postexploratory checks

Following exploration of the CBD, many surgeons wish to check duct clearance by either postexploratory T tube cholangiography or choledochoscopy. The main drawback of the former is difficulty in obtaining a technically satisfactory cholangiogram. Air bubbles are a common problem and contrast often does not enter the duodenum after instrumentation of the ampulla[36] (a procedure that should always be done as little as possible and with great care). When a good normal cholangiogram is finally obtained, the incidence of retained stones falls to zero[27,37]. The alternative method of visualizing the duct after exploration is choledochoscopy using a rigid or flexible instrument; the results are similar for either instrument[38]. There are many consistent reports showing that postexploratory choledochoscopy virtually eliminates retained stones[38–41]. The technique of choledochoscopy is quickly learnt and we perform it routinely after CBD exploration. In all the quoted series, postoperative T tube biliary drainage was still performed followed by cholangiography 7–10 days later. This allowed decompression of the biliary tree until any ampullary oedema settled, provided an easy means of checking for retained stones, and also created a track for possible stone extraction should this be necessary. Opinions vary as to whether postoperative T tube cholangiography is still required after choledochoscopy[38], but we are not aware of any major series where this view has been adopted.

Treatment of retained stones

Retained stones may be dissolved or removed via the T tube or its track, extracted via an endoscopic sphincterotomy or removed by a further operation.

Gallstone dissolution

Dissolution via the T tube using sodium cholate was first reported by Way *et al.*[27]. Although success rates of up to 60 per cent were achieved by flushing with bile salts[42], side-effects, particularly diarrhoea, can be severe. Mono-octanoin (a solvent for cholesterol) is another agent that has been used extensively but without the side-effects of bile salts. Although several reports have claimed success rates of up to 80 per cent, the number of patients were small. Perhaps the most useful and illuminating report is that by Palmer and Hoffman[43] who reported the results in 343 patients. In 26 per cent there was complete disappearance of the stones, partial dissolution sufficient to allow extraction endoscopically or via the T tube track occurred in 29 per cent, and no change was seen in the remainder. Treatment had to be aborted in 9 per cent of patients because of side-effects.

We no longer practise gallstone dissolution, largely because of the much better results obtained with extraction via the T tube track and endoscopic sphincterotomy. In hospitals without these extraction facilities dissolution may be attempted but it is probably quicker and more effective to refer the patient to a centre practising stone extraction.

Extraction via T *tube track*

This method of stone removal was first described in 1959 by Mondet. In expert hands 95 per cent of stones can be extracted by this technique[44,45], but the success rate falls to 58 per cent when less than 10 procedures are performed in a year[46]. Complications occur in 5 per cent of patients and the technique is limited by large stones (which must be crushed before extraction), a small diameter T tube track, or multiple small stones in a dilated CBD. Furthermore, the procedure cannot be carried out until a mature sinus track has formed and this usually takes 6 weeks.

Removal via endoscopic sphincterotomy (compared with reoperation)

Endoscopic sphincterotomy was developed 12 years ago by Classen and Demling[47] and most surgeons now at least have access to the technique even if they do not practise it themselves.

Initially used for the treatment of retained stones, and latterly for the initial management of CBD stones, endoscopic sphincterotomy is now an established and successful method of managing choledocholithiasis. In skilled hands, a sphincterotomy can be successfully performed in about 95 per cent of patients and 90 per cent of these will have successful extraction of stones from the CBD giving an overall figure of 85 per cent for duct clearance (*Table 1*). The 15 per cent failure rate after initial sphincterotomy may fall with time as a proportion of stones will pass spontaneously or be removed at a second attempt. This should be compared with surgical exploration where the incidence of surgical failure, i.e. retained stones, averages 4 per cent[32] but the ease of a second attempt at removal is rather less than the endoscopic equivalent. Following endoscopic sphincterotomy for residual stones, complications occur in 5–8 per cent of patients and consist of bleeding, pancreatitis, cholangitis and retroperitoneal perforation[48–51]. One per cent of patients require emergency surgery and the overall mortality is one per cent. In comparison, the mortality of a second operation on the CBD for stones, although less well documented, ranges from 0 to 2 per cent[1,55,56]. The incidence of recurrent stones or stenosis after endoscopic sphincterotomy during follow-up of up to 7 years is 4–10 per cent[57–59]. This is probably an adequate follow-up period as restenosis mainly occurs within 1 year of endoscopic sphincterotomy[60]. Comparative results following surgical bile duct exploration are available. The Mayo Clinic found that 5 per cent of 208 patients who had CBD stones removed previously required surgery for further biliary problems during a 5-year follow-up[61]. However, the recurrent stone rate after *re*-exploration of the common bile duct ranges from 18 to 83 per cent[52,62,63] depending on the number of previous choledochotomies. If an internal drainage procedure is performed these figures are considerably reduced. Transduodenal sphincteroplasty is one such procedure and when performed for recurrent stones (the surgical equivalent to endoscopic sphincterotomy—although both may vary in the size of opening), Lygidakis[64] found that 12·5 per cent of patients developed stenosis or recurrent stones. It is important to remember that the effectiveness of both surgical and endoscopic methods depends on the exact technique used.

At present, endoscopic sphincterotomy is slightly less successful at clearing CBD stones than surgery, but the incidence of recurrent stenosis or stones in comparative surgically treated patients is similar. Because of this and the minimal discomfort and inconvenience of endoscopic sphincterotomy, patients with retained stones should seldom require reoperation where highly skilled endoscopy is available. However, a definitive operation by an experienced surgeon is far preferable to repeated inadequate attempts to extract the stone endoscopically. Factors weighing heavily against successful endoscopic clearance after sphincterotomy are the presence of a stricture below the stone, a tortuous CBD and stones greater than 20 mm in diameter (although stones larger than 20 mm are

Table 1 *Success and complication rates of endoscopic sphincterotomy performed for calculi*

Reference	Author	Attempted sphincterotomies	Successful sphincterotomies	Overall percentage of ducts cleared	Morbidity	Mortality
48	Classen and Safrany 1975	59	50	84%	2%	0%
49	Safrany 1978	3853	3618	90%	7%	1·4%
50	Cotton and Vallon 1981	679	590	76%	8·5%	1%
51	Siegel 1981	235	230	97%	5%	0·8%
52	Cotton and Vallon 1982	71	70	87%	6%	0%
53	Neoptolemos *et al.* 1984	100	98	91%	13%	1%
54	Hatfield 1985	256	241	85%	9·5%	0%

being removed by experienced endoscopists). Surgery will usually be required in these patients.

Prevention of recurrent stones

Surgery for recurrent or residual calculi is technically demanding and is best avoided. We have already reviewed current methods of reducing the incidence of retained stones to very low levels. The aetiology of recurrent CBD stones is biliary stasis. Several factors that indicate stasis can be recognized at the first operation[65]: sludge or gravel in the CBD, friable irregular CBD stones, failure of contrast to enter the duodenum in the absence of an impacted stone, and chronic pancreatitis associated with a degree of ductal obstruction.

When should internal surgical biliary drainage be performed?

There is good evidence to suggest that, in the presence of biliary stasis, the incidence of recurrent stones ranges up to 80 per cent[62,63]. Thus any patient who is recognized to have biliary stasis at the first operation, as well as those who have uncleared hepatic duct stones, multiple CBD stones (e.g. more than five) or an impacted stone in the ampulla, should have internal drainage. Patients who have residual stones requiring surgery have an increased operative risk[1] and, in order to minimize the chance of a further operation, these patients too should have internal drainage.

Which biliary drainage procedure should be performed?

Two standard procedures are commonly performed – choledochoduodenostomy and transduodenal sphinctero-plasty. Both procedures have their advocates but in the only prospective trial of the two procedures, choledochoduodenostomy was considerably better[64]. One hundred and twenty patients with recurrent choledocholithiasis either had exploration without internal drainage, or exploration combined with choledochoduodenostomy or transduodenal sphincteroplasty.

Twenty-two per cent of those who had exploration alone required further surgery for recurrent stones compared with 12 per cent of those who had transduodenal sphincteroplasty and none of the patients undergoing choledochoduodenostomy. The incidence of recurrent cholangitis was 2·5, 27·5, and 2·2 per cent respectively. These figures support our own view that choledochoduodenostomy is the internal drainage procedure of choice unless common bile duct diameter is less than[66] 15 mm, stones are impacted in the ampulla, or there is a history of recurring pancreatitis associated with CBD stones[67]; in these circumstances transduodenal sphincteroplasty is more suitable.

We have applied the policy of internal biliary drainage described above to all patients in our unit undergoing choledochotomy. During the last 5 years, 105 choledochotomies were performed of which 5 were reoperations and of these 41 patients underwent choledochoduodenostomy. One patient (2·5 per cent) died of a myocardial infarct. No bile leaks occurred and during a median follow-up of 3 years no complications have occurred. Over a longer follow-up of 5–20 years, others have found that the mortality rate as well as the incidence of recurrent cholangitis averages 3 per cent or less[68–70]. the so-called 'sump syndrome' occurring after choledochoduodenostomy is ill defined, but is thought to result from debris or bacteria accumulating in the CBD distal to the site of choledochoduodenostomy[70,71]. In order to avoid this the stoma must be at least 2·5 cm in diameter to allow free passage in and out of the CBD; if it occurs, the sump syndrome can be treated by endoscopic sphincterotomy[72].

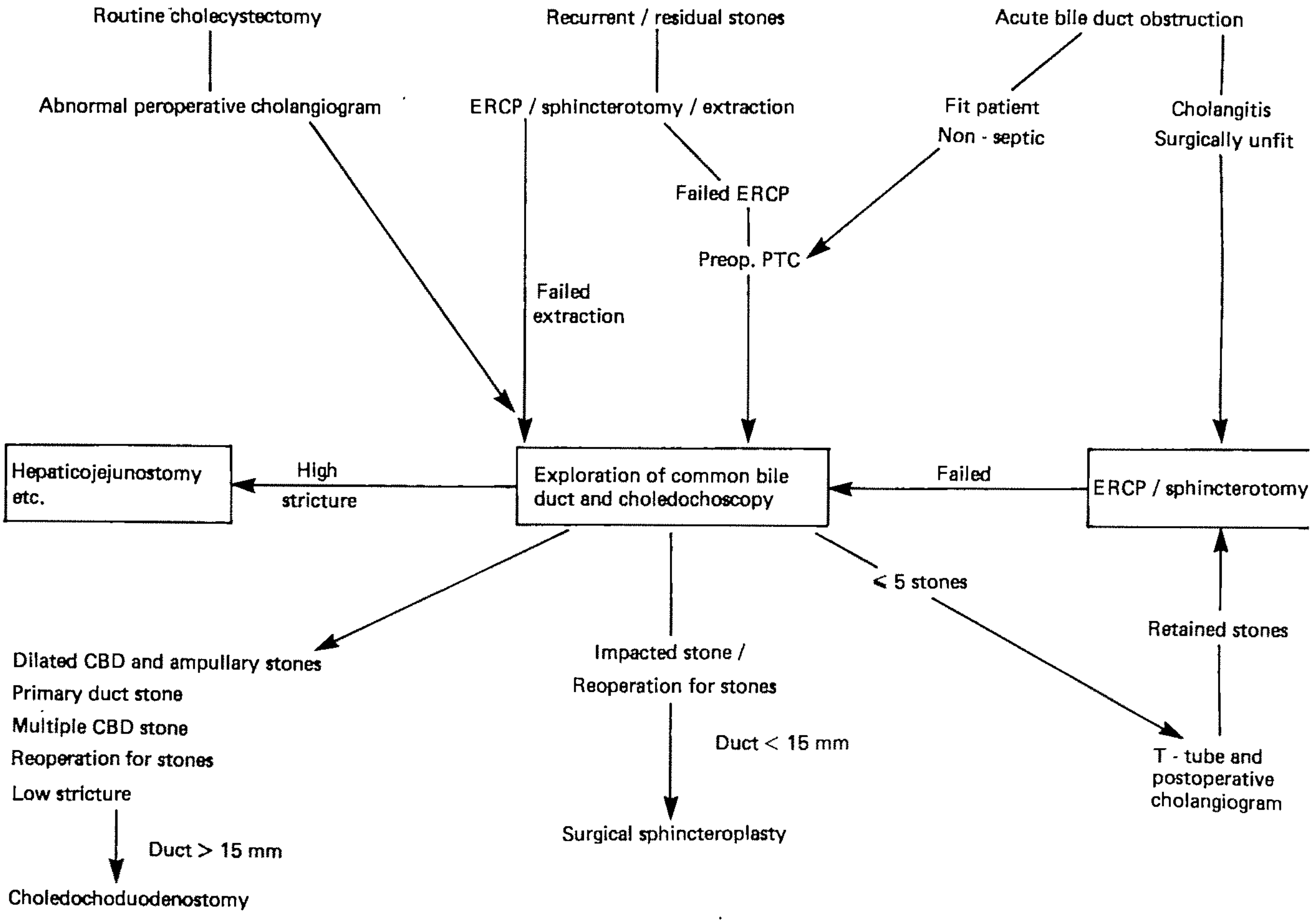

Figure 1 *Management of patients with choledocholithiasis*

Pre-operative drainage of the CBD

Considerable changes have occurred in the management of acute obstruction of the CBD. The risk of operating on a patient with cholangitis is considerable, particularly if the patient is elderly. In elderly patients the mortality of biliary tract surgery performed electively is acceptable at 0–2 per cent but in the emergency situation rises to 12–19 per cent[3,73]. Over the years endoscopic sphincterotomy has been used increasingly to relieve obstruction caused by stones or ampullary stenosis and permit the patient's condition to improve before performing elective surgery later. Cotton and Vallon[52] reported their experience of 71 patients (average age 75 years) with gallbladders *in situ* who underwent endoscopic sphincterotomy for urgent symptoms including jaundice, gallstone pancreatitis, cholangitis and biliary colic. Sixty-one patients (86 per cent) had their duct cleared of stones and symptoms settled in 59 patients. Large stones were the commonest cause of failure to clear the CBD but surgery was safely carried out in these patients. One patient who was totally unfit for surgery died. Similar results have been reported from Leicester[53]. Although some of the younger patients went on to have elective cholecystectomy, many of the older patients were considered unfit for a further procedure. Within this latter group, 10 per cent in Cotton and Vallon's series and 4 per cent in the Leicester study required subsequent cholecystectomy with no mortality. In elderly patients the staged procedure of endoscopic sphincterotomy possibly followed by cholecystectomy when the patient's condition permits has good evidence to support it.

Subsequent cholecystectomy is not always necessary but if it is required, this is usually within one year of endoscopic sphincterotomy.

Intrahepatic calculi

Stones in the hepatic ducts are uncommon in the Western world but they can cause serious morbidity. It is important that any examination of the biliary tree is adequate to document or exclude their presence. Principles of treatment have been established from the extensive experience gained in Eastern Asia[74,75] and are equally applicable in Western surgery. These principles are to remove as many stones as possible; provided all stones have been removed and there is no associated stricture, nothing further need be done. Should stones remain in the absence of a stricture, choledochoduodenostomy or sphincteroplasty is performed. If strictures are present, these must be dealt with in order to prevent cholangitis and recurrent stones.

Strictures

In any patient with choledocholithiasis, bile duct strictures must be looked for and excluded. Failure to recognize a stricture is likely to cause recurrence of stones. It is unusual to encounter a stricture at the first choledochotomy but this will be revealed by peroperative cholangiography. More often benign strictures present after previous biliary surgery and are best delineated by PTC[76]. Although ERCP is an acceptable alternative, we prefer PTC as the proximal extent of the stricture is well seen and allows better planning of surgery. The type of operation performed depends on many factors and is beyond the scope of this review. The best results are achieved in a specialist centre[77] and patients should be referred to these centres for this type of surgery.

The results of this survey are summarized in the flow chart (*Figure 1*). Although individual surgeons will naturally have minor variations we suggest that this is a rational approach based on the information and expertise now available. Each group of gastroenterologists and surgeons must develop a plan of management based on local expertise and facilities – surgical, radiological, and endoscopic – so that treatment does not depend on the whim of a particular clinician on a particular day. Moreover, the philosophy that maintains that any procedure is justified if it avoids an operation must be challenged. Operation may well be the simplest, quickest and even the safest way of removing duct stones.

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Paper accepted 31 January 1987

Br. J. Surg. 1987, Vol. 74, July, 561–563

Carcinoma arising in posterior pharyngeal pulsion diverticulum (Zenker's diverticulum)

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Carcinoma is a rare but recognized complication of posterior pharyngeal pulsion (Zenker's diverticulum). Such diverticula merit radiological and endoscopic examination before operation. Surgery is preferred to radiotherapy in the treatment of carcinoma, the choice of operation resting between one-stage diverticulectomy for cancer confined to the body of the sac and pharyngolaryngectomy for more extensive lesions.

Keywords: Pharyngeal diseases, pharyngeal neoplasms, hypopharyngeal neoplasms, oesophageal diverticula

The first case of a posterior pharyngeal pulsion diverticulum was described by Mr A. Ludlow of Bristol[1] in 1764. Over the following century and a half many more cases were described, but the first successful excision was not carried out until 1886, when Wheeler[2] removed a lateral pharyngeal pouch and a posterior pharyngeal pulsion diverticulum from the same patient. Shlesinger (cited by Halstead[3]) reported a carcinoma arising in a posterior pharyngeal pulsion diverticulum in 1903, but the first report in the English literature was by Vinson[4] from the Mayo clinic in 1927, though Kelson[5] in 1921 reported a carcinoma arising at the site of excision of a diverticulum 7 years previously. This led to an increasing awareness that these diverticula, especially when longstanding, might be the site of carcinoma *in situ* or squamous cell carcinoma.

Incidence

Since 1927 there have been 38 cases reported in the English literature including two cases described in this article (*Table 1*). The case described by Sparks[6] is the same patient as that reported by Capps and Dunhill[33] and mentioned by Dunhill[34]. Similarly the case reported by Lewis and Edwards[35] is the same as one of the cases mentioned by Turner[16]. A further case mentioned by Baker[36] is not included as the site of the diverticulum is not clear. The age at diagnosis of a carcinoma in the sac has always been over 50, with a range 50–89 years and a mean of 67·7 years, in the 35 patients on whom data were available. The sex distribution is 33 men and 5 women, giving a ratio of 6·6:1.

Many of the reported patients form part of small series, giving an incidence of between 2·6 per cent[10] and 6·7 per cent[12], but in larger series the incidence appears to be much lower. Wychulis[19] in 1969 reported 3 patients with carcinoma in a series of 961 patients from the Mayo Clinic, an incidence of 0·3 per cent. This series was reviewed in 1984 by Huang *et al.*[30] who reported two further carcinomas in 1249 cases, an incidence of 0·4 per cent. Mackay[25] reported 1 case in 92 patients and Hoover[8] 2 cases in 185 patients, both reports giving an incidence of 1·1 per cent, while other authors with large series[37–39] have reported no cases of carcinoma. Carcinoma arising in a diverticulum is thus uncommon but cannot be ignored, the true incidence probably being between 0·5 per cent and 1·5 per cent.

We have had 2 cases in a series of 53 patients, an incidence of 3·7 per cent. The first was a 70-year-old man who had sudden onset dysphagia for solids but no other symptoms. Barium swallow demonstrated a large diverticulum which was subsequently excised. Histology showed a carcinoma *in situ*. The patient died a year later from natural causes.

The second case was a 50-year-old man with a large diverticulum diagnosed 10 years previously but not treated, who presented with rapidly progressive dysphagia and weight loss. Oesophagoscopy and biopsy confirmed a squamous cell carcinoma in a large diverticulum. He underwent a total pharyngolaryngectomy with reconstruction, but died on the fourth postoperative day of a secondary haemorrhage from the left common carotid artery.

Aetiology

The aetiology is obscure but is thought to be associated with patients having longstanding diverticula. Huang *et al.*[30] reported an average duration of symptoms of 11·7 years. In 28 cases of this review in whom duration of symptoms was given, the average was 14·0 years. The sac was described as large in 62·5 per cent of patients, though carcinoma may also arise in small diverticula[27,29].

Chronic irritation and inflammation of the sac wall due to retention and stasis of food debris have been implicated in carcinomatous change in the sac and have certainly resulted in other histological changes, including ulceration[40]. This theory was propounded because chronic irritation was considered to be the predisposing factor in carcinomatous change in other areas of the body such as chronic leg ulcers and ulcerative colitis[13,20]. In achalasia of the cardia, chronic irritation from stagnation of food is thought to contribute to the high level of malignant change[41]. Lieberson and Riese[14], while discussing histology, state that malignant changes were found in 'a mucosa with extensive inflammatory changes, disturbance of normal maturation of cells and leukoplakia', which seems to support the above theory.

Clinical presentation

The presentation of most patients with a carcinoma arising within a diverticulum is identical to that of an uncomplicated diverticulum; there are however a few characteristic features. A sudden change in the severity of the normal symptoms is quite typical of these patients, in particular progressive dysphagia or aphagia. They often complain of more marked regurgitation of sac contents which sometimes contain blood, indeed haematemesis may be the presenting sign as in cases described by Lieberson[14] and by Fischer[17]; of the cases reviewed 26·5 per cent had blood in the sac contents[6,9,14,15,17,19,20,28] (*Table 1*). Weight loss is a frequent finding but is also common in uncomplicated diverticula. Eight patients [6,11,12,13,15,19,25,28] complained of a lump in the neck which is more common than in series of uncomplicated diverticula. Pain is an unusual symptom but highly suggestive of malignant change, and has been described in three patients[9,11,28].

0007–1323/87/070561–03$3.00

Table 1 *Reported cases of carcinoma of Zenker's diverticulum*

Author(s)	Age	Sex	Duration of symptoms	Blood in sac contents	Weight loss	Treatment	Results
Vinson[4]	63	M	10 years	—	+	Attempted excision + DXRT	Died of Ca 5 months
Sparks[6]	59	M	30 years	+	+	Excision	Died of haemorrhage 8 days
Fitzwilliams[7]	55	M	8 years	—	—	Excision of Ca + DXRT	Died of abscess 3–4 months
Hoover[8]	56	M	10 years	—	+	Partial pharyngolaryngectomy	Alive and well 3 months
2nd case				No details given			
Morley[9]	57	M	16 years	—	+	Exploration	Died of Ca 5 months
	78	M	40 years	+	+	Exploration	Died of pneumonia 24 h
Dohlman[10]				No details given		Dohlman's	Not given
Bullock and Snyder[11]	66	M	3 years	—	+	Excision	Alive and well 5 months
Lindskog and Stern[12]	82	M	5 years	—	—	Block excision	Not given
Riberi *et al.*[13]	82	F	20 years	—	+	Excision	Alive and well 15 months
Lieberson and Riese[14]	62	M	Several years	+	—	Excision + DXRT	Died of Ca 'several' months
Garlock and Richter[15]	70	M	8 years	+	—	Excision + DXRT	Alive and well 14 months
Turner[16]	63	M	30 years	—	—	DXRT + excision	Alive and well 6 months with recurrence
	82	F	3 years	—	+	Dohlman's	Not given
Fischer and Bond[17]	67	M	20 years	+	—	Exploration + DXRT	Died of Ca 27 months
Som and Dietel[18]	76	M	6 years	—	+	Excision	Alive and well 18 months
Wychulis *et al.*[19]	58	M	25 years	+	—	Excision + DXRT	Died of Ca
	89	M	16 years	+	—	Excision	Died of Ca 4 months
	64	M	5 years	—	+	Excision	Died ? cause 19 months
Pierce and Johnson[20]	55	M	10 years	+	—	Excision	Alive and well 36 months
Juby[21]	50	M	24 years	—	—	Pharyngolaryngectomy	Died of Ca 18 months
Knight and Gautam[22]	68	M	2 years	—	—	Excision	Not given
Kune[23]	57	M	20 years	—	—	Excision	Alive and well 60 months
Hansen *et al.*[24]				No details given		Excision	Died of MI 55 months
Mackay[25]	65	M	11 years	—	+	Biopsy + DXRT	Died of Ca *x* months
Nanson[26]	80	M	20 years	—	+	Excision	Alive and well 36 months
Rojas *et al.*[27]	67	M	Months	—	–	Excision + DXRT then pharyngolaryngectomy	Alive and well 10 months
Donald and Huffman[28]	55	F	20 years	+	+	Pharyngolaryngectomy + DXRT	Alive and well 36 months
Zonnevylle *et al.*[29]	73	M	2 months	—	+	Excision	Alive and well 12 months
Huang *et al.*[30]	80	F	—	—	—	Excision	Alive and well 96 months
	70	M	25 years	—	—	Excision	Alive and well 51 months
Johnson and Curtin[31]	62	M	Many years	—	+	Exploration + DXRT + CXT	Not given
Bakaka and Sadek[32]	76	M	Years	—	+	Excision	Alive and well
	75	M	2 years	—	—	Excision + DXRT for recurrence	Alive and well 60 months
	85	F	Years	No details given		DXRT	Died shortly of Ca/pneumonia
Author's	70	M	Months	—	+	Excision	Died of natural causes 6 months
	54	M	4 years	—	—	Pharyngolaryngectomy	Died of haemorrhage 5 days

DXRT, radiotherapy; CXT, chemotherapy; Ca, carcinoma; MI, myocardial infarction

Investigation

Plain radiology may show a suspicious widening of the retropharyngeal space[25,31] but investigation is normally by contrast radiography. Barium fills the sac which may show a filling defect due to carcinoma, but food debris, if inspissated, mimics this appearance. However, food and air shadows are generally seen in the upper part of the diverticulum, whereas the shadow of a carcinoma will be found in the fundus or lateral wall of the diverticulum, usually in the lower two-thirds[16]. Carcinomas have occasionally been reported arising at the neck of the sac[9,15,17]. The radiological appearances of a carcinoma are a constant filling defect, continuous with an otherwise smooth-walled diverticulum; if this appearance is constant on repeat swallows the likelihood of a carcinoma is increased. It is worth noting that carcinoma *in situ* does not alter the smooth outline of the diverticulum[11,29]. However, owing to the difficulty of interpretation, only six cases have been directly diagnosed from radiographs. Turner in an excellent review of the radiographs of previously reported cases was able to identify a carcinoma retrospectively in almost all cases.

We consider oesophagoscopy to be an essential part of the investigation, either as a separate procedure where there is a high index of suspicion, or as the first stage of definitive surgery. The diverticulum should be carefully cleaned and examined prior to passing a nasogastric tube and packing the diverticulum. In 13 of the reported cases the diagnosis has been established at oesophagoscopy. However, more often the diagnosis has been made incidentally during open surgery or by the pathologist[22,27].

The histology is usually squamous cell carcinoma though variations have been found such as basal cell or spindle cell carcinoma[24] and carcinoma *in situ*, of which there have been five cases reported[11,29,32] including one of the patients reported by the authors. Benign tumours may also arise in a diverticulum[16].

Treatment and results

Most of the cases have been reported individually rather than as series so that it is difficult to determine a uniform method of treatment. Furthermore the lack of full follow-up information

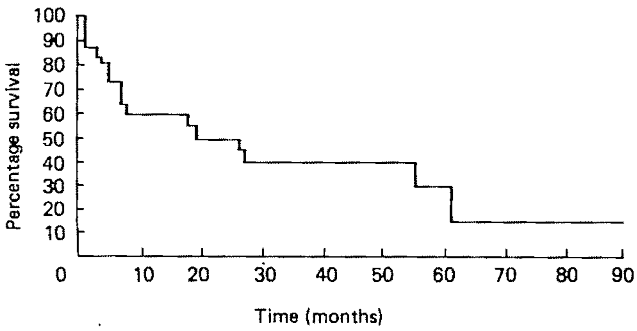

Figure 1 *Crude survival in carcinoma of pharyngeal pouch*

prevents complete accuracy in evaluating the survival.

Twenty-three patients were treated by one-stage diverticulectomy, five of whom had postoperative radiotherapy and one pre-operative radiotherapy[16]. Fourteen were reported as alive and well at follow-up, the longest survival being 96 months after surgery[30], though one patient had a subsequent recurrence treated by a pharyngolaryngectomy[27]. Radiotherapy did not appear to help.

Five patients underwent a pharyngolaryngectomy: three were alive and well at between 3 months and 36 months[8,27,28], one died of recurrent disease after 18 months[21], and one of our own patients died of a postoperative haemorrhage.

Seven patients had inoperable lesions: five received radiotherapy[4,17,25,31,32] and two had a gastrostomy[9]. Six died after a few months but no information was available on one patient who had received radiotherapy. A further seven patients received radiotherapy either following one-stage diverticulectomy or pharyngolaryngectomy. On one patient the outcome was not reported and the other six died after between 4 and 60 months[7,14,15,17,32].

Seven cases were found after other surgical procedures: four following a Dohlman's procedure[10,16,21,25], two following a diverticulopexy[7,12] and the last following a cricopharyngeal myotomy[26]. Of the two remaining patients there was insufficient information on treatment[8,12]. Data on outcome were available in 31 cases, and were analysed for crude survival. The 3-year survival was 39 per cent but the 5-year survival only 14 per cent (*Figure 1*). Radiotherapy is of doubtful value as excision of the pouch is indicated on the grounds of symptoms alone, even without the added complication of a carcinoma.

In summary, careful examination of a diverticulum by radiological investigation and endoscopic examination is indicated before operation. Treatment by radiotherapy alone is not associated with a good prognosis and there is insufficient evidence to suggest whether it increases survival following surgery. The main method of treatment has been one-stage diverticulectomy, often because the diagnosis was not made until after histological examination; however, it can be curative. When a diagnosis is made prior to surgery we believe that one-stage excision is still indicated provided that the carcinoma is confined to the body of the sac without involvement of the diverticulo-oesophageal septum. When the neck of the diverticulum or the diverticulo-oesophageal wall is involved, more extensive resection by a pharyngolaryngectomy is indicated.

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Paper accepted 4 March 1987

Br. J. Surg. 1987, Vol. 74, July,
564–566

Restorative proctocolectomy: the four loop (W) reservoir

The four loop (W) reservoir was developed with the aim of improving the functional results of the J reservoir and to avoid the need for catheterization often seen with the S reservoir. It is no more difficult to construct and results in better function. Sixty-four patients have undergone the procedure. There were no deaths. Mean hospital stay (including ileostomy closure) was 24 ± 8 days. The reservoir has been removed in one patient (one week postoperatively) who was found to have a Dukes' B rectal carcinoma. Function has been assessed in 51 patients (mean follow-up $18{\cdot}6 \pm 8{\cdot}9$ months). Frequency of defaecation per 24 h is $3{\cdot}3 \pm 1{\cdot}0$ (range 1–8) with night evacuation in 14 per cent. Antidiarrhoeal medication is required by 20 per cent of patients. Continence is normal in 92 per cent, and 8 per cent have minor leakage. All patients defaecate spontaneously.

Keywords: Proctocolectomy, ulcerative colitis, familial adenomatous polyposis

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Restorative proctocolectomy has been used successfully in selected patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP)[1]. The procedure removes all diseased mucosa and prevents the need for an ileostomy. Several changes have been made since Parks' original three loop (S) reservoir[2] in an effort to improve function as assessed by frequency of defaecation, night evacuation, continence and the need for catheter evacuation. The use of a two loop (J) reservoir[3] eliminates the need for catheterization but is associated with a significantly higher frequency of defaecation and night evacuation[4]. The four loop (W) reservoir results in both spontaneous defaecation and improved function. Construction of the W reservoir is no more difficult, being two Js placed side by side.

We present the clinical results obtained with the W reservoir and describe the operative technique in detail.

Patients and methods

Operative technique

The patient is positioned as for synchronous combined excision of the rectum. The abdomen is explored through a long midline incision. The procedure is divided into three stages including (1) removal of the colon and rectum, (2) construction of the reservoir and (3) perineal excision of the anorectal mucosa with ileo-anal anastomosis. A defunctioning loop ileostomy has been used in all cases.

The colon is removed in a routine fashion. Below the rectosigmoid junction the dissection is carried out close to the rectal wall. The two leaves of the mesorectum are separated and the branches of the superior rectal artery are ligated piecemeal to avoid damage to the presacral and parasympathetic nerves. After washing out the anorectal stump with povidone-iodine, the bowel is transected at the level of the anorectal junction, leaving an anorectal stump of about 3–4 cm in length.

Before constructing the ileal reservoir a trial descent of the ileum to the dentate line is made. An assistant takes up a position facing the perineum. The ileum is folded into two loops, each 12 cm long, with the apex at the most dependent point (*Figure 1*). Two stay sutures are placed at this point, and are drawn down through an opened retractor by the assistant. If the apex of the loop reaches the dentate line at this stage then it will reach after the reservoir has been made. The ileocolic vessels are routinely divided to gain additional length. Rarely selected vessels in the arcade which are under tension require division.

In constructing the reservoir, the ileum is folded to make four loops, creating two apices with the second lying 2 cm proximal to the first. A series of Babcock clamps is placed on the loops to secure their position (*Figure 1*). Three rows of continuous seromuscular sutures are then inserted as shown, and the four loops are opened on their antimesenteric border using the cutting diathermy to minimize bleeding (*Figure 2*). A continuous all-layers suture is placed between adjacent loops. The front of the reservoir is closed in two layers leaving an opening for the anastomosis of a diameter that will comfortably take two fingers (*Figures 3,4*).

In performing the mucosal proctectomy an anal retractor is passed to display the anorectal stump, which should be only 3–4 cm in length. A solution of normal saline containing adrenaline in a dilution of 1/300 000 is injected submucosally to lift the mucosa from the muscle layer. The mucosa is then excised from the level of the dentate line to the edge of the divided rectum using sharp-pointed scissors, taking care to avoid damage to the internal sphincter.

The anastomosis is then made between the opening in the reservoir and the anal canal at the dentate line using interrupted sutures of 2/0 polyglactin (Vicryl) mounted on a heavy duty taper cut 25 mm needle. Two such sutures are placed on the left and right sides of the opening by the abdominal surgeon, leaving the needle on the suture. The perineal operator then inserts an anal retractor and passes two long artery

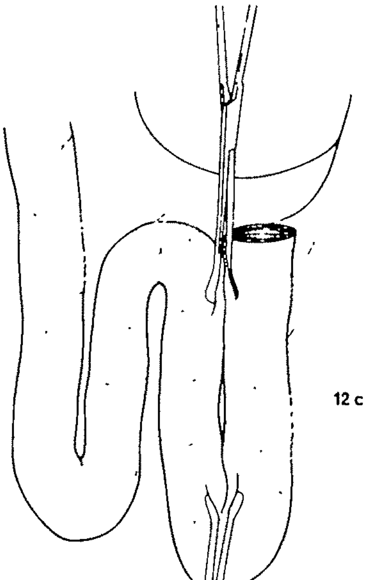

Figure 1 *The terminal ileum is folded, initially for trial descent to the dentate line, and later to make four loops*

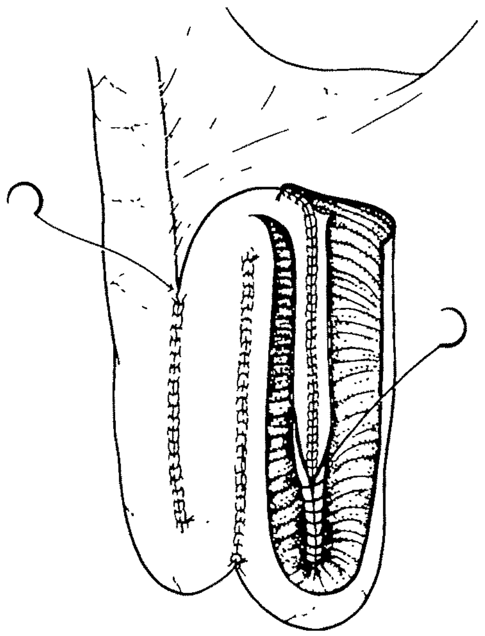

Figure 2 *The loops of ileum are opened and adjacent loops sutured*

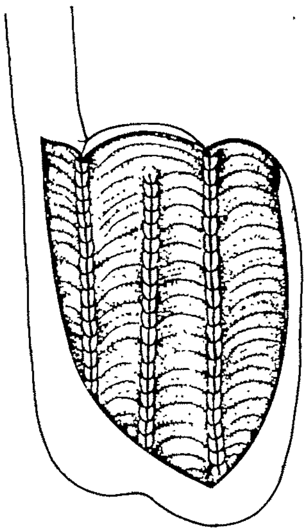

Figure 3 *Completed suture of adjacent loops with front of reservoir ready for closure*

forceps in turn through the anus into the pelvic cavity to grasp them. They are then delivered through the anal canal, the needles are taken in a needle holder and the sutures are placed at the dentate line on each side. When these sutures are tied the reservoir is drawn down into the anal canal to this level. Two further sutures are placed per anum, one anteriorly the other posteriorly, and it is then possible to insert the anal retractor into the lumen of the reservoir. By this manoeuvre the edge of the opening of the reservoir and the dentate line become well exposed and are usually seen to be approximated. The ileo-anal anastomosis is completed by inserting about 8–10 further sutures. These include the anoderm of the anal canal with a bite of internal sphincter, and the full thickness of the reservoir wall. The pelvis is drained with a suction drain. brought out through the abdominal wall and a temporary loop ileostomy is made in the right iliac fossa using the previous ileostomy trephine if already present.

Patients

Sixty-four patients underwent the procedure between March 1983 and March 1986. There were 28 males and 36 females. The mean age was 29 ± 10 years (range 14–52 years). Fifty-seven had UC, six FAP and one functional bowel disease. There were no deaths. The reservoir was removed in one patient who had had a colectomy with ileostomy and preservation of the rectal stump 14 years previously, giving a failure rate of 1·6 per cent. This was carried out a week postoperatively since pathological examination had revealed unforeseen malignancy in the excised rectal stump. The patient had had longstanding colitis and stenosis of the rectum had prevented adequate sigmoidoscopic examination. Six patients had not yet had the ileostomy closed and in six it has been closed less than one month before this assessment. Function was assessed in the remaining 51 patients at a mean of 18·6 ± 8·9 months from closure of the ileostomy. The patients were followed up in the outpatient department at 3–6 monthly intervals and details of bowel frequency, continence and medication were obtained. For the purpose of this assessment they were personally interviewed and examined by one of the authors (D.Z.L.) and not by the other (R.J.N.).

Statistical methods

Student's *t* test was used in the analysis of the mean values of normally distributed data. Percentage values were compared by calculating the standard error of the difference between the two proportions. A difference was taken to be significant if it was greater than two standard errors.

Results

Complications

There were four cases who developed partial dehiscence of the ileo-anal anastomosis (6 per cent) (*Table 1*). Healing occurred spontaneously by secondary intention in all. Intestinal obstruction due to adhesions requiring laparotomy with eight cases (13 per cent) was the most important complication. An anastomotic stricture occurred in four cases requiring dilatation (none occurring in those patients with anastomotic dehiscence), and in two patients a fistula-in-ano was laid open.

Function

The mean frequency of defaecation per 24 h was 3·3 ± 1·0 (s.d.) with seven patients (14 per cent) having night evacuation on more than one occasion per week (*Table 2*). The range of

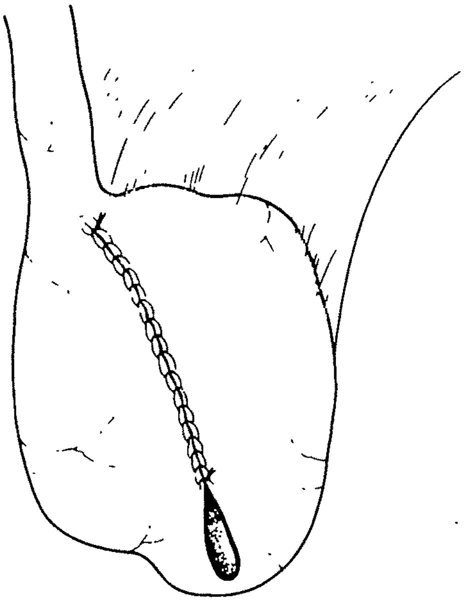

Figure 4 *Front of reservoir with opening for ileo-anal anastomosis*

Table 1 *W reservoir: complications in 64 patients*

Pelvic sepsis	4 (6%)
Intestinal obstruction (laparotomy)	8 (13%)
Wound infection	8 (13%)
Haemorrhage (laparotomy)	1
Water and electrolyte depletion	4
Stricture and dilatation	4
Fistula-in-ano	2
Optic atrophy	1

Table 2 *W reservoir: function in 51 patients*

Follow-up (months)	18·6±8·9
Frequency/24 h	3·3±1·0
Night evacuation > 1/week	7 (14%)
Catheter evacuation	0
Medication	10 (20%)
Continence	
Normal	47 (92%)
Minor leak (pad)	4 (8%)
Faecal leak	0

frequency was 1–8 per 24 h. Continence was normal in 47 patients (92 per cent) and the remainder had minor soiling consisting of a smear requiring the use of a small pad. There was no case of failure of erection or ejaculation and all had normal urinary function. All patients defaecated spontaneously. Mean total hospital stay, including the admission for closure of the ileostomy, was 24±8 days. The interval from the reservoir operation to the ileostomy closure was 2·2±1·1 months.

Discussion

Restorative proctocolectomy is a safe procedure and the operative morbidity has fallen with experience[6]. In particular, ileo-anal anastomotic dehiscence is now infrequent. It is said anastomotic complications occur less frequently with a short rectal cuff[5,6] and the experience in the present series supports this. However, the possibility exists that increased experience may account for this improvement in morbidity. The incidence of obstruction has not fallen when compared with the earlier experience of the operation at the same hospital.

Fifty-four per cent of the patients with S reservoirs need to catheterize due to the distal ileal segment[7]. The incidence of catheterization has been reported to be lower if a shorter distal ileal segment is used, and Goldberg[6] found only 8 per cent and Cohen[5] 1 of 60 patients required catheterization. Nevertheless, by anastomosing the W reservoir directly to the anal canal the need for catheterization is completely eliminated.

In our experience with 17 J reservoirs (M/F = 13/4; UC/FAP/functional disease = 13/3/1; age 35±10 years) the frequency of defaecation has been relatively high (mean 5·5±1·4) and significantly greater than with the W reservoir (mean 3·3±1·0; $P<0·001$). Similarly the frequency of night evacuation has been greater for the J (57 per cent) compared with the W (14 per cent) reservoir in our experience. Although the series of W reservoir reconstructions followed that of the J reservoirs, the improved results of the former are unlikely to be due to a learning curve phenomenon. The J reservoirs themselves were made after a series of 16 S reservoirs performed by one of the authors which, with a mean frequency of 3·7±1·4/24 h, were also functionally superior to the J reservoirs. In addition, taking the first 17 W reservoirs, function is much better (mean frequency 3·0±0·9) than the J reservoirs. Despite the lack of randomization the difference in function given the absence of learning curve phenomenon is very significant. Similar results with the J reservoir have been reported by Dozois of a mean frequency of defaecation 6·0±2·6 daily and 1·2±1·3 at night[4]. There is every indication that capacitance/compliance characteristics of the reservoir influence function and studies from our unit have demonstrated lower frequency in relation to greater compliance and higher maximum tolerated volume[8]. Similar studies from the Mayo Clinic[9] have related capacitance/compliance to frequency following straight ileo-anal anastomosis.

The functional results obtained in the patients reported here support the general view that a long rectal muscle cuff is not necessary for continence[6]. We regard leaving a short cuff as important since removal of the anorectal mucosa is greatly simplified, and theoretically the risk of leaving behind nests of rectal mucosa is diminished[10].

Damage to the presacral sympathetic nerves may result in retrograde ejaculation. This complication has occurred in 9 per cent of patients when the rectum is mobilized posteriorly in the anatomical plane[4], and is particularly important given the benign nature of the disease and young age of most of these patients. With a close rectal dissection as used in the present series, however, we have had no case of altered sexual or bladder function and therefore feel this to be an important aspect of technique. The dissection takes longer and is more difficult but if pelvic nerve injury can be avoided, as appears to be the case, then it must be preferable to a conventional dissection.

The W reservoir uses 40–50 cm of terminal ileum. This is a similar amount to three 12–15 cm loops of the S reservoir[2,11] or two 20 cm loops of the J[3,6]. It is no more difficult to construct, being two Js joined together. By arranging the two limb pairs to be offset, the ileoanal anastomosis is similar to that with a J reservoir. Although the opening for the anastomosis is at the distal end of the opening in the front wall of the reservoir and therefore has a suture line incorporated in the anastomosis, this has not adversely affected the leak rate. The W reservoir is no more difficult to bring down to the anus and in our experience results in better function.

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Paper accepted 6 March 1987

Br. J. Surg. 1987, Vol. 74, July,
567–568

Mathematical prediction of ileal pouch capacity

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Restorative proctocolectomy is an operation still in the stage of development. Three main types of ileal pouch construction are used, but the advocacy of each probably arises more from familiarity and convenience than from scientific considerations. Since, other things being equal, pouch capacity can be expected to affect stool frequency, it seemed reasonable to examine calculable pouch capacity geometrically for different methods of construction. A mathematical model was therefore used to compare the double loop ('J') type with the quadruple loop ('W') construction. The W was estimated to have a capacity more than half as great again as the J. Similarly anastomotic methods which encroach on the ileal circumference by creating an inverted edge can be expected to reduce resultant capacity by 10 per cent or more.

Keywords: Restorative proctocolectomy, ileal pouch

Restorative proctocolectomy seems, from early reports, set fair for wide usage. The procedure though will undoubtedly undergo modification before the best method emerges.

Details of pouch construction for instance are controversial. Some authorities favour the double loop ('J') method, some the triple ('S') and others the quadruple ('W'); again some surgeons counsel a two layered suture line, others a single layer appositional closure, and others stapling where possible. The advocacy of each, though, seems idiosyncratic rather than scientific in inspiration. Since pouch volume can reasonably be supposed to affect stool frequency, and since a superficial analysis suggests that the W pouch in more nearly approaching a sphere in shape would accommodate the greatest volume for the same length of ileum, there seemed to be merit in attempting to determine theoretical pouch capacity for purposes of comparison.

Method

Since both J and W pouches can reasonably be treated as closed cylinders for purposes of theoretical volumetric measurement, the one long and narrow, the other short and wide, a mathematical model can be used to compare their possible volumes using geometric formulae.

The model consists of a cylinder length a and radius r which is closed by curving the ends inwards along the arc of a circle of the same radius as the cylinder (*Figure 1*). Now the surface area of a segment of cylinder is given by the formula $2\pi rh$ where h is its length and r the radius. If, as in our model, $r=h$, then the surface area of the cuff of cylinder used to close the ends is $2\pi r^2$, which is the formula for the curved surface area of a hemisphere. Therefore, by using cylinder cuffs length r the model is closed by perfect hemispheres and so its volume can be deduced simply as a volume of the two hemispheres, $4/3\pi r^3$, plus the volume of the intervening residual cylinder, $\pi r^2(a-2r)$ (*Figure 1*).

Applying our calculations clinically (using a 40 cm ileal loop), the value for a is 20 cm in the J and 10 cm in the W. The value for r can be derived from the measurable ileal circumference, which we can temporarily call b cm, from the formula circumference $(b)=2\pi r$. As the J pouch uses two ileal circumferences, its radius $=b/\pi$, and the radius of the W pouch, incorporating four ileal circumferences $=2b/\pi$.

Substituting these values for r in our basic formula for pouch volume

$$\frac{4}{3}\pi r^3+\pi r^2(a-2r)$$

we can give the J pouch volume ($a=20$ cm) as

$$\frac{4}{3}\pi\left(\frac{b}{\pi}\right)^3+\pi\left(\frac{b}{\pi}\right)^2\left(20-\frac{2b}{\pi}\right)$$

which resolves to:

$$\frac{2b^2(30\pi-b)}{3\pi^2}$$

Similarly, the W pouch volume ($a=10$ cm) is

$$\frac{4}{3}\pi\left(\frac{2b}{\pi}\right)^3+\pi\left(\frac{2b}{\pi}\right)^2\left(10-\frac{4b}{\pi}\right)=\frac{8b^2(15\pi-2b)}{3\pi^2}$$

To find the volume of each type of pouch now only needs a value for b, the ileal circumference.

Gray's Anatomy[1] describes the ileum as having a diameter of 3·5 cm. However, it is a matter of daily operative experience to observe that the ileum is not, unless obstructed, an inflated tube of some 11 cm circumference. The value given almost certainly refers to the external measurement of its width (and even so is on the large side) and so is in fact its external hemicircumference. We have found the internal circumference of the opened unobstructed terminal ileum to be about 5 cm. In our calculations, therefore, values for b of 5 cm and 7 cm have been used. These give pouch capacities of 150·7 cm^3 and 288·8 cm^3 respectively for the J, and 250·8 cm^3 and 438·5 cm^3 for the W. Therefore, the theoretical pouch capacity for quadruple loop construction exceeds the double loop by 66·4 per cent given an internal ileal circumference of 5 cm, and 51·8 per cent for 7 cm.

Supposing the internal circumference to be as great as 7·854 cm, the quadruple loop construction in our mathematical model forms a perfect sphere (in other words there is no residual intervening cylinder) whose

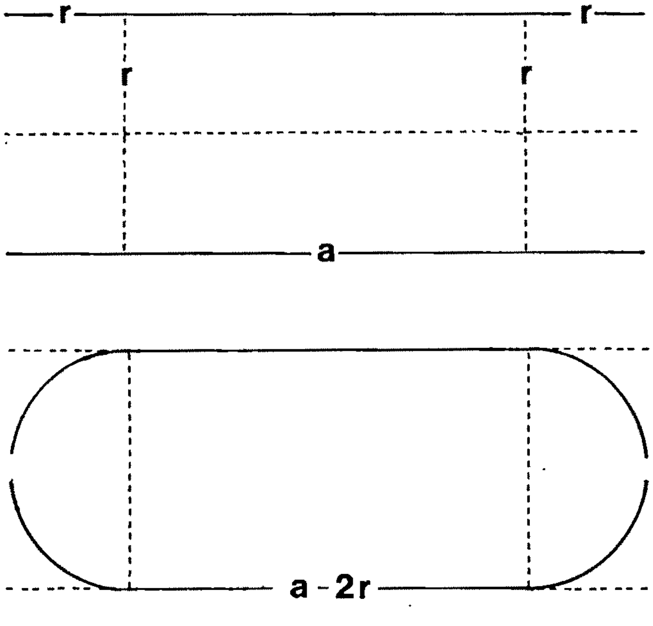

Figure 1 *Basis for mathematical model for calculation of pouch capacity*

volume is 523·6 cm^3, which is 45·4 per cent greater than the volume achieved by double loop construction (360·0 cm^3) with that ileal circumference. Given greater values for ileal circumference, the model becomes a wide sphere with amputated poles, so that were the ileal circumference 11 cm as *Gray's Anatomy*[1] suggests, the pouch would be wider than it was long (14 × 9·17 cm) which is demonstrably not the case.

If in the mathematical model the cylinder ends are incompletely closed to allow apertures corresponding with the anal anastomosis and the afferent loop, and volumes deduced for the resulting 'amputated' hemispheres by integral calculus, the differences in overall volumes are less than 5 cm^3. Therefore, the calculations being much more complicated, such considerations have been left out of our presentation.

Effect of anastomotic technique

Our calculations have assumed the anastomosis to have been made by one layer edge to edge apposition. Using staples or a two-layer suture method a small but measureable portion of the ileal circumference will thereby be incorporated as an inverted edge and so be lost to the pouch wall. If we suppose it to be 2 mm at each edge the J construction will lose 4 × 2 mm and the W 8 × 2 mm.

With appropriate subtraction in our equations for 5 cm circumference loops resultant pouch capacities are 128·1 cm^3 and 216·8 cm^3 respectively for J and W constructions, a reduction of 22·6 cm^3 (15·0 per cent) and 34·0 cm^3 (13·6 per cent).

Discussion

Our calculations support the premise that in more nearly approaching a sphere the W pouch will provide the greatest volume for any given length of ileum. Conversely, the narrower the ileal loop the more marked the reduction in J pouch capacity. The figures given for capacity are 'resting' ones; in life the volume accommodated will depend on many factors, but could, given the elasticity of the ileal wall, be much larger. Assuming bowel frequency to reflect pouch capacity (other things being equal) we conclude that quadruple loop construction will give better 'value for money' than the double (or triple) and that fashioning with one layer extramucosal appositional anastomoses will be preferable to edge-inversion closure methods.

Acknowledgements

The first author wishes to acknowledge that the idea for this mathematical exercise was stimulated by Mr R. J. Nicholls' observation (personal communication) that a quadruple pouch should have the greatest capacity in approaching more closely the spherical.

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Paper accepted 23 March 1987

Br. J. Surg. 1987, Vol. 74, July,
569–572

Five year results of a randomized trial of adjuvant 5-fluorouracil and levamisole in colorectal cancer

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Following curative surgery for colorectal cancer 141 patients were randomized to receive a 6 month course of 5-fluorouracil (5FU) with or without postoperative levamisole or supportive treatment only. The patients have been followed up for a minimum of 5 years and 52 per cent of patients in the control group, 44 per cent of the 5FU group and 32 per cent of the 5FU/levamisole group have died of tumour recurrence. This represents a significant survival advantage in the patients receiving levamisole, even when other patient and tumour factors are allowed for.

Keywords: Colorectal cancer, 5-fluorouracil, levamisole

Surgery for colorectal cancer is followed by a 50 per cent recurrence rate even when a curative resection has been performed[1,2]. The hope that adjuvant chemotherapy would reduce the risk of recurrence remains unfulfilled. 5-fluorouracil (5FU) has been most investigated; however, with the exception of administration via the portal route[3], 5FU has been worthless as an adjuvant chemotherapeutic agent in this disease. Following an early report of success in the use of the immunostimulant drug levamisole in lung cancer[4], and our finding that levamisole shortens the duration of postoperative immunosuppression if given early in the postoperative period[5], we have studied whether the restoration of immunity by levamisole would improve the results of adjuvant 5FU on tumour recurrence and patient survival following surgery for colorectal cancer.

Patients and methods

Patients

One hundred and forty-one patients with colorectal cancer were randomized to one of three treatment groups following surgery. Patients over the age of 80, patients with serious intercurrent illness, patients with a history of previous malignancy and those presenting as an emergency were excluded. Pre-operative assessment was by chest radiography, liver enzyme estimation and a sulphur colloid radioisotope liver scan. Patients with abnormalities suggesting metastases were excluded, as were patients with operative findings of liver secondaries or macroscopic residual tumour following resection.

Following surgery the patients were treated in a routine manner. Nasogastric intubation was not routinely used; however patients who had a nasogastric tube and who received levamisole had the tube spigotted for 4 h following administration of the drug. All patients have been followed up by one of the authors (R.W.) until death or for a minimum of 5 years. Follow-up was by clinical examination and monthly haematology while on 5FU and by 6 monthly chest X-ray, liver enzyme estimation, radio-isotope scan and carcinoembryonic antigen levels.

Treatment groups

Group A received supportive treatment only and acted as controls. Group B received 1 g 5FU intravenously following surgery and on the first two postoperative days, followed by 1 g orally weekly for 6 months. Group C received, in addition to 5FU as in group B, 150 mg levamisole orally on the first three postoperative days.

Immunological studies

In order to show that the patients treated with postoperative levamisole had a more rapid return of cellular immunity, *in vitro* leucocyte migration inhibition to BCG and tumour antigen was estimated (LMIT) in the first 20 patients in each group. LMIT was performed pre-operatively and at 3 and 7 days following surgery and weekly thereafter until normal. The techniques used have previously been described[5].

Statistical evaluation

The difference in the return of LMIT following surgery between treatment groups was assessed using the Mann–Whitney *U* test. Kaplan–Meier's product limit method was used to estimate the survivor functions for the three treatment groups. Patients who died from other causes and those who survived to the end of the study were treated as censored data[6]. The difference between survivor functions for the three groups was assessed using the Mantel–Cox statistic. Proportional hazards models were then used to investigate the effect of the treatments on survival time when account was taken of the other patient factors as covariates[7].

Results

There were four postoperative deaths in group A, three in group B and three in group C. These patients have been excluded from analysis, leaving 45 evaluable patients in group A, 42 in group B and 44 in group C.

The three treatment groups were well matched for age and sex (*Table 1*), for performance status, duration of symptoms before presentation and weight loss (*Table 2*), for site of primary (*Table 3*) and for tumour stage and differentiation (*Table 4*). In

Table 1 *Patient groups*

	Control	5FU	5FU/levamisole
Total	49	45	47
Evaluable	45	42	44
Median age in years (range)	60 (44–75)	63 (44–76)	58 (28–79)
Male:female	23:22	18:24	26:18

Table 2 *Patient details*

	Control	5FU	5FU/levamisole
Performance status			
0	26	24	33
1	19	18	11
Symptoms (months)			
<6	18	21	22
6–12	18	11	16
>12	9	10	6
Weight loss			
<5%	23	24	30
5–10%	18	14	8
>10%	4	4	6

addition, operative and postoperative factors which might have had a possible bearing on survival have been studied (*Table 5*). These include the type of operation (abdominoperineal excision or restorative resection) used for tumours of the rectum, blood transfusion immediately before, during or within 3 days of surgery and further surgery in the form of staged colostomy closure. Finally, patients in each treatment group who required anticoagulation for deep venous thrombosis (27 patients) or for a heart valve prosthesis (one patient in group B) were looked at. At the time of the study, prophylactic heparin was not being used and proven deep venous thrombosis was treated with between 5 and 10 days of heparin followed by 3 months of warfarin. Using the χ^2 analysis (with Fisher's correction where applicable) there was no significant difference between the three groups for any of these factors.

Immunological studies

Five of the twenty patients in the 5FU/levamisole group who were tested had a return of LMIT to pre-operative levels at 3 days and the remaining fifteen patients demonstrated a return of LMIT at 7 days. With regard to the patients who did not receive levamisole, LMIT was restored to pre-operative levels in group A patients by 7–42 days (median 21 days) and in group B patients by 7–56 days (median 27 days). There was no statistical difference in the restoration of LMIT between these two groups. However the difference in the return of LMIT between the patients receiving levamisole and the two groups of patients not receiving levamisole was statistically significant ($P = 0{\cdot}001$).

Patient survival

All patients who developed a recurrence of tumour have subsequently died of their disease. Death was due to recurrence in 20 of 45 patients (44 per cent) in group A (control), in 22 of 42 patients (52 per cent) in group B (5FU) and in 14 of 44 patients (32 per cent) in group C (5FU + levamisole). Survivor functions were estimated for the three treatment groups and the differences between the survivor functions for groups C and A and those for groups C and B were significant ($P = 0{\cdot}046$ and $P = 0{\cdot}022$ respectively). There was no significant difference between the survivor functions for groups A and B (*Figure 1*).

A series of Cox proportional hazard models was fitted using, as covariates, all factors other than treatment in order to obtain a group of patient and operative factors which independently and significantly affected survival. To this was then added treatment with 5FU and 5FU and levamisole as separate covariates. This demonstrated that increasing stage of tumour ($P < 0{\cdot}0001$), decreasing duration of symptoms ($P < 0{\cdot}0001$) and receipt of blood ($P = 0{\cdot}0166$) all had a significantly detrimental effect upon survival at the 5 per cent level. When these and all the other non-significant variables were allowed for, treatment with a combination of 5FU and levamisole continued to have a significantly beneficial effect on survival ($P = 0{\cdot}0024$).

The pattern of recurrence was similar in each of the three treatment groups. Local recurrence was observed first in eight patients in group A (40 per cent), in eight in group B (36 per cent) and in five patients in group C (36 per cent). Pulmonary metastases were found in three patients in group B and in four patients in group C. In the remaining patients (12 in group A, 11 in group B and 5 in group C) hepatic spread was the first sign of recurrence.

Toxicity

Significant drug toxicity was observed in both groups B and C (*Table 6*). Neutropenia with counts below 4×10^9/l was seen

Table 3 *Site of primary*

	Control	5FU	5FU/levamisole
Right colon	8	8	9*
Transverse colon	3	2	2
Left colon	7	8	2
Sigmoid colon	8	8	12*
Upper rectum	11	12	10
Lower rectum	8	4	10

* 2 primaries

Table 4 *Tumour details*

	Control	5FU	5FU/levamisole
Stage			
2 (into muscularis)	4	4	3
3 (to serosa)	11	10	5
4 (through serosa)	9	11	22
5 (invasion locally)	6	5	0
6 (nodes involved)	15	12	14
Differentiation			
Well	8	0	8
Moderate	34	32	30
Poor	3	10	6

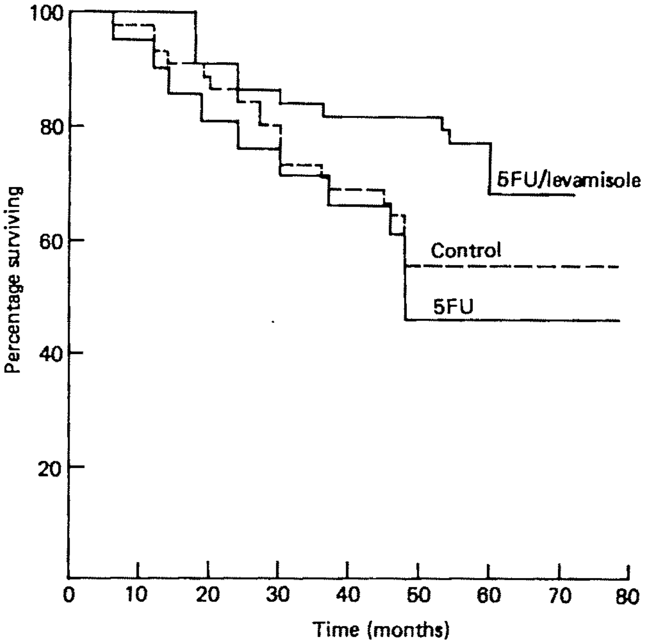

Figure 1 *Survivor functions for the three treatment groups. For control and 5FU/levamisole groups* P = *0·046 and for 5FU and 5FU/levamisole groups* P = *0·022 (Mantel–Cox)*

Table 5 *Operative details*

	Control	5FU	5FU/levamisole
Abdominoperineal excision	8	5	10
Anterior resection of rectum	11	11	10
Perioperative transfusion	21	21	16
Subsequent colostomy closure	9	8	5
Long-term anticoagulation	9	7	12

Table 6 *Complications*

	5FU	5FU/levamisole
Alopecia	6	6
Neutropenia $<4\times10^9$/l	12	10
Nausea	14*	10
Drug associated death	0	1

* Led to early termination

following the three postoperative doses of 5FU in 29 per cent and 23 per cent of groups B and C respectively. Three patients in group B and four in group C developed profound neutropenia with counts below 1×10^9/l. 5FU was stopped until the counts had returned to normal. This was usually by 1 week in the patients with mild neutropenia and by 1 month in those with severe neutropenia. There was one patient death in group C from pancytopenia associated with postoperative sepsis following an anastomotic leak. There was no further neutropenia following weekly 5FU. Nausea following 5FU was a recurrent problem in a total of 24 patients and led to 1 patient in group B being unable to complete the 6 month course of 5FU. Alopecia during 5FU treatment was seen in a total of 12 patients and led to the need for a wig in 8 women.

Discussion

Depression of immunity has a detrimental effect, independent of stage, on the prognosis of malignant disease[8,9]. Despite this, attempts to stimulate immunity have met with only sporadic success in cancer treatment[10,11] and efforts have concentrated on the development of a more effective application of chemotherapy and radiotherapy. In colorectal cancer these modalities have made only a small impression on the natural history of the disease[3,12].

If stimulation of the immune system is to be of any possible therapeutic benefit, logically it should be applied where there is already a depression of immunity and where tumour load is small. Therefore we have studied the use of immunotherapy following surgery for colorectal cancer, when it is well established that there will be depression of immunity[13] and where, despite an absence of macroscopic residual disease, as many as 50 per cent of patients will be expected to have micrometastases.

The immunostimulant chosen was levamisole which is easily administered orally and known to restore cellular immunity depressed by surgery[5,14–16]. After commencement of the trial, evidence emerged of a possible detrimental effect on survival associated with levamisole[17]. This led us to terminate accrual early and at a time when the trial may have had insufficient numbers to show a statistical difference between treatment groups. Depsite this we have shown a significant survival advantage in the administration of levamisole with 5FU following surgery for colorectal cancer. This survival advantage remained when other factors significantly affecting survival were controlled for. These included tumour stage, which was inversely related to survival, and duration of symptoms before presentation, which was directly related to survival. In addition, the administration of blood during the perioperative period had a detrimental effect on survival, as has been found by other workers[18,19]. Although immune restoration was not confirmed in all patients receiving levamisole, the patients who were tested so closely followed our previous experience of levamisole in this situation[5], that we chose to dispense with immune evaluation in the remainder of the series. The beneficial effect of levamisole was therefore presumably related to the rapid restoration of immunity at a time when tumour bulk has been reduced to a minimum by surgery. Administration of chemotherapy at this point may be expected to give the best opportunity for a therapeutic response. Levamisole alone has been reported to be of benefit in lung cancer[4]. However a subsequent study has failed to confirm this[17] and the use of levamisole alone probably has little place in cancer treatment. However levamisole as an adjuvant to a treatment which causes immunodepression may be of more value. Certainly the administration of levamisole during radiotherapy for breast cancer has led to a prolongation of disease free interval in post menopausal patients, when compared with radiotherapy alone[20]. Also when given immediately before surgery for gastric cancer, levamisole has been shown in two studies to improve the results of postoperative chemotherapy[21,22]. In each of these studies the patients with minimal residual disease but at most risk from recurrence benefited, namely the stage 2 breast cancer patients and those with stage 3 stomach cancer. Not all chemotherapeutic drugs will cause such a profound depression of cellular immunity as does surgery or radiotherapy and this may explain the lack of success obtained by Bancewicz *et al.*[23] using a combination of 5FU and levamisole in colorectal cancer patients. In their study, the drugs were given for 1 year but were not begun for 4–6 weeks following surgery. By that time cellular immunity would be virtually restored to normal and 5FU would be unlikely to suppress it further[24]. By using a very short course of levamisole we seem to have avoided the adverse effects on the cardiorespiratory system observed by Anthony *et al.*[17]. Neutropenia has been observed with levamisole[25], however we did not see a greater incidence of this complication than with 5FU alone.

In conclusion we have found that a short postoperative course of the immunostimulant drug levamisole together with a 6 month course of adjuvant 5FU reduces the recurrence rate in colorectal cancer. Because of the small size of this study, its results must be interpreted with caution. However a complex relationship does exist between the host, a cancer and its treatment and for the success of the latter, greater consideration may need to be given to the immune status of the former. Our results and those cited above[20–22] suggest that in this context levamisole is worthy of further investigation.

Acknowledgements

The authors would like to acknowledge with thanks the following surgeons who allowed their patients to be included in the trial: Mr W. W. Barrie, Mr J. F. Bolton Carter, Mr A. W. Hall, Mr J. M. S. Johnstone, Mr D. W. Watkin, Mr K. F. Wood and Professor R. F. M. Wood.

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Paper accepted 30 March 1987

Announcement

Overseas Doctors Training Scheme (Surgery)

At the request of the Department of Health and Social Security (DHSS), the Royal College of Surgeons of England is setting up a training scheme in general surgery and orthopaedics for doctors from abroad. This will be under the arrangements for double sponsorship introduced by the General Medical Council. The posts included in the scheme will be established National Health Service posts subject to the DHSS Terms and Conditions of Service and with Royal College recognition. In the main overseas doctors will be appointed to rotational programmes of surgical training, where possible including University Teaching Hospitals, in regions throughout England and Wales, and Northern Ireland. The principle aim of this scheme is to provide a high standard of surgical training for doctors outside the United Kingdom and the European Community to help them in their work when they return home. Further particulars can be obtained from the ODTS office, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK.

Br. J. Surg. 1987, Vol. 74, July, 573–575

Risk of colorectal cancer after surgery for benign peptic ulceration

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A historical prospective cohort study has been conducted to determine the incidence of colorectal carcinoma following gastric surgery for benign peptic ulcer disease. A total of 4131 patients from 53 hospitals in the western part of Denmark were operated upon for gastric or duodenal ulcer from 1955 to 1960 inclusive. After exclusion of patients who were diagnosed as having a primary cancer before the ulcer operation and 0·5 per cent of the patients whose present status could not be defined, 2975 men and 943 women survived more than one month after the operation and thus formed the cohort of the study. They were followed up to their death or the end of the year 1982. Eighty-four colorectal carcinomas were observed against the expected 85·9. There was no significant difference between observed or expected number of cancers neither among men nor women.

Keywords: Gastric surgery, colorectal carcinoma, stomach, peptic ulcer disease

The surgical treatment of peptic ulcer disease has been associated with an increased risk of subsequent gastric cancer in several studies[1–5] although this association is still debatable[6–10]. The suggested increase in risk is related especially to partial gastrectomy with a Billroth II anastomosis[2,4,5] or to gastrojejunostomy.

In a case-control study of 289 patients with colorectal cancer matched to 289 randomly selected control patients with respect to age, sex and date of admission Bundred *et al.*[11] have found an increased prevalence of previous peptic ulcer surgery in colorectal cancer patients. Three other studies[12–14] have revealed an increased mortality from colorectal cancer among patients who have undergone gastric surgery for peptic ulcer. These studies have been based on relatively few ulcer surgery patients[11] or have concerned only dead patients who had previously undergone ulcer surgery. Therefore it has been considered valuable to publish a historical prospective cohort study about the incidence of colorectal cancer after peptic ulcer surgery. The study is a part of a continuing larger study of the incidence of all cancers after peptic ulcer surgery.

Patients and methods

The records of patients operated on for benign peptic ulcer disease during the period 1955–60 in the western part of Denmark were examined by the author. Information was abstracted from records in 53 hospitals covering a population of about 2·5 million people. In a further three hospitals the files had been burned or had disappeared. Site of ulcer, type of operation performed and date of operation were registered together with name, sex and birth date.

Records were abstracted for 4164 patients of whom 33 were excluded because of insufficient identifying information, leaving 4131 patients (3139 men and 992 women) for analysis. Of these, 29·7 per cent had gastric ulcers, 62·3 per cent had duodenal and pyloric ulcers and 8·0 per cent had ulcers in other sites (jejunum, multiple ulcers, gastritis). The operations performed were: in 69·1 per cent of cases a Billroth II subtotal gastrectomy; in 10·8 per cent a Billroth I resection; in 0·9 per cent a vagotomy with drainage; in 2·7 per cent a gastrojejunostomy alone and in 14·5 per cent a simple suture of a perforated ulcer. In 2 per cent various other operations were performed (*Table 1*).

The cohort was followed with regard to death by computerized record linkage with the Central Population Registry in existence since 1968, the National Death Registry in existence since 1943 and through direct contact with general practitioners, priests and municipality based population registers. The patients in the cohort with cancers were then found through The Danish Cancer Registry.

The Danish Cancer Registry is a population based national cancer registry founded in 1942. Incidence rates are available since 1943. Reports are received on all newly diagnosed cancers in Denmark and the registration can be regarded as complete[15–17] and similar to compulsory cancer registration schemes where completeness has been assumed[18]. The Registry is tumour based, and recorded cancer cases are classified according to an extended version of the seventh revision of the International classification of Diseases (WHO 1957) as described in detail by Jensen *et al.*[19].

The number of cancers in the cohort were obtained from The Cancer Registry by record linkage. Patients with cancers diagnosed before or within one month of ulcer operation and patients who did not survive the ulcer operation were excluded. Person-years at risk were calculated from the time of operation until the diagnosis of cancer, date of death, 31 December 1982, or age 100 years whichever occurred first[27]. Expected numbers were computed by multiplying the person-years at risk in 5 year age and calendar periods with the corresponding incidence rates for colorectal cancers in all of Denmark, thereby adjusting indirectly for age and calendar time effect when summed over the cells[20]. Relative risks (RR) were obtained by dividing the observed by the expected number of cases, and 95 per cent confidence limits of the RR were calculated assuming a Poisson distribution[21].

Table 1 *Site of ulcer and type of operation*

	Billroth II	Billroth I	Gastrojejunostomy	Perforation suture	Vagotomy	Other
Gastric	696	178	7	293	3	51
Duodenal	1907	205	103	303	36	20
Gastritis	151	49	0	0	0	3
Other	99	13	2	5	0	7
Total	2853	445	112	601	39	81

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Table 2 *Observed and expected (O/E) colorectal carcinomas by 5 year intervals with relative risk (RR) and 95 per cent confidence limits in parentheses*

Follow-up interval	0–4 O/E	5–9 O/E	10–14 O/E	15–19 O/E	20–24 O/E	⩾25 O/E
Men	8/10·8	13/12·9	9/14·4	11/14·8	17/11·2	0/1·7
RR	0·75 (0·3–1·4)	1·0 (0·5–1·7)	0·62 (0·3–1·2)	0·74 (0·4–1·3)	1·5 (0·9–2·4)	0·0 (0–2·2)
Women	3/3·3	7/3·8	6/4·2	6/4·5	4/3·7	0/0·5
RR	0·9 (0·2–2·6)	1·8 (0·7–3·7)	1·4 (0·5–3·1)	1·3 (0·5–3·5)	1·08 (0·3–2·7)	0·0 (0–7·2)
Total	11/14·1	20/16·7	15/18·6	17/19·3	21/14·9	0/2·2
RR	0·8	1·2	0·8	0·9	1·4	0

Table 3 *Observed and expected (O/E) number of colorectal cancers in patients with Billroth II gastrectomy followed by 5 year intervals*

Year	0–4 O/E	5–9 O/E	10–14 O/E	15–19 O/E	20–24 O/E	⩾25 O/E
Men	5/7·3	11/9·1	8/10·3	10/10·7	12/8·2	0/1·3
Women	2/2·3	5/2·6	3/3·0	5/3·2	3/2·7	0/0·4

Results

Seventeen (½ per cent) of the original cohort could not be found in any registers either because of errors in the original records or because they had disappeared and were excluded from the investigation. Fifty-eight men and twenty-seven women had cancers diagnosed before or within one month of ulcer operation and 106 men and 21 women did not survive the operation. This left for analysis 2975 men and 944 women—a total of 3919 persons. Person-years at risk for these individuals were 67 220 years (men, 51 020 years; women, 16 200 years), a mean of 17·15 observation years for both men and women.

A total of 84 colorectal carcinomas were diagnosed (men 58, women 26) between the time of operation for peptic ulcer and 31 December 1982 against 85·9 carcinomas expected (men 65·9, women 20·0). The relation between observed and expected cancers and RR in 5 year periods is seen in *Table 2*. The majority of patients had a Billroth II procedure performed. In these patients the observed number of colorectal cancers was 64 (men 46, women 18) against 61·1 (men 46·9, women 14·2) (*Table 3*).

Discussion

Some investigations have shown a relationship between cholecystectomy and cancer of the large bowel[22–25]. The major factors in this latter relationship are considered to be alterations in intestinal bile salts, dietary fats and bacterial flora[26,27]. Similar alterations have been observed in the intestine after gastric surgery[28–31] and thus gastric surgery might subsequently lead to an increased risk of colonic cancer. On the other hand the fact that ulcer surgery leads to a faster passage of the food through the bowel and thereby a shorter exposure of the colonic mucosa to possible carcinogens subsequently might lead to a decreased risk of colonic cancer.

Bundred *et al.*[11] suggested that an alteration in faecal bile acids following vagotomy and drainage, which is similar to that seen following cholecystectomy[29], might explain their findings of an increased incidence of colorectal cancers. The altered bacterial flora in the stomach after gastric surgery[30,31] may also lead to a breakdown of bile acids into metabolites, which could promote colon carcinogenesis. The vagal effect at the colonic mucosal cell turnover is influenced by a total abdominal vagotomy and less from a conventional partial gastrectomy, and therefore the carcinogenetic effect from various surgical procedures may be different.

In the first 20 years after the ulcer operation there is no significant increase in the incidence of colorectal cancers—even if there seems to be a small difference between men and women. In some of the 5 year periods there may even be a small protective effect. From 20 to 24 years there is a small increase, but this tendency is not seen further on after 25 years, and is not considered to be real.

The total number of patients studied, the several different ulcer operations, and the fact that both gastric and duodenal ulcers were involved means that this study is similar to others. For completeness of analysis the present material has been subdivided into different types of operation and the relative risk of colorectal cancer has been computed. However, this does not change the results in any of the subgroups.

In this historical prospective cohort study with some 4000 patients with collection of information for up to 27 years after surgery for benign peptic ulceration, no increase in incidence of colorectal carcinomas was found. This finding applies to the whole study group with several different types of operations performed, but also applies to the largest group of operations (Billroth II resections). Naturally the conclusion is less valid for the operations with a smaller number of patients (e.g. vagotomy with drainage).

Acknowledgements

I thank the involved hospital departments for access to patient records. The Danish Cancer Registry has been very helpful in the follow-up and has maintained the statistical analysis. The study was supported by grants from The Danish Cancer Association (28/79).

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Paper accepted 31 March 1987

Br. J. Surg. 1987, Vol. 74, July, 576–579

Physiological study of pruritus ani

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Physiological abnormalities in the anorectum of 34 patients with pruritus ani, and 20 age and sex matched controls were assessed. A saline infusion (1500 ml) test showed that leakage started after infusion of 600 ml in patients with pruritus ani compared with 1300 ml in controls (median values: $P<0{\cdot}001$). There was an inverse relationship between the severity of the symptoms of pruritus ani and the volume of first leakage on the saline infusion test $P<0{\cdot}02$. Studies to assess anal sphincter function, rectal sensation to balloon distension, rectal compliance, and perineal descent did not show any significant differences between pruritic patients and controls. However, pruritic patients without co-existing anal pathology had a significantly greater fall of anal pressure when a rectal balloon was inflated (57 per cent) when compared with controls (40 per cent) $P<0{\cdot}05$.

Keywords: Pruritus ani, saline infusion test, anal manometry

Pruritus ani is a common and disabling condition, but its pathogenesis is poorly understood. Persistent pruritus ani is often associated with an underlying dermatological or anal pathology, but transient pruritus ani is commonly idiopathic[1]. Minor leakage of faecal material through the anal canal may cause perianal soiling, predisposing to excoriation of perianal skin. Matters are often made worse if patients are then prescribed topical preparations containing a local anaesthetic or antibiotic since they may induce an allergic dermatitis[2]. The purpose of this study was to attempt identification of an underlying defect of anal sphincter function in patients with pruritus ani using manometric and radiological techniques.

Patients and methods

Thirty-four consecutive patients with long-standing pruritus ani refractory to prolonged measures designed to improve perianal hygiene were studied. Twenty-five patients were men (73 per cent), and nine were women. Their median age was 48 years (range 23–71). Results were compared with a control group consisting of 20 individuals of comparable age with no history of pruritus ani and no known gastrointestinal disease. These individuals were either attending for hernia repair ($n=17$) or were volunteers from the medical staff ($n=3$). Thirteen controls were male (65 per cent), their median age was 53 years (range 25–86). The median number of vaginal deliveries among the nine pruritic women was two (range 1–7). The corresponding median for the seven female control subjects was two (range 0–3).

Clinical assessment

Clinical assessment included history and rectal examination, proctoscopy and sigmoidoscopy. On clinical history none of the patients was noted to be suffering from diarrhoea. Within the pruritic group, 14 patients had a completely normal anal canal, and 20 had a variety of one or more anal conditions: haemorrhoids ($n=17$), skin tags ($n=4$), anal fissure ($n=2$), anterior mucosal prolapse ($n=3$) and non-specific proctitis ($n=1$). No individual in the control group had any anal disease as assessed by proctosigmoidoscopy.

Assessment of severity of pruritus ani

The severity of perianal itching was assessed, in the first 13 patients, by the use of a linear analogue scale with a range from 0 to 10. On arrival in the clinic, patients were asked to consider how severe their perianal itching had been over the previous 7 days. This was then indicated by the patient on the linear scale.

Microbiological cultures

The perianal skin of all subjects in the study was examined using an ultraviolet light (Wood's lamp) to detect the characteristic cutaneous fluorescence of *Corynebacterium minutissimum*. In addition, Sellotape® was placed on the perianal skin and then applied to a microscope slide to exclude infection of the skin from ova, cysts, and parasites. Perianal skin scrapings were taken from each patient and cultured on Saberaud's medium for 6 weeks to exclude mycotic infections.

Saline infusion test

Anal sphincter competence for fluids was assessed in all patients in the study using a saline infusion test[3]. An 8F Foley catheter was introduced through the anal sphincter into the rectal ampulla. Then 1·5 litres of 150 mM NaCl was infused through the catheter at a rate of 50 ml/min, using a constant infusion pump over 30 min. The patient was seated on a commode over a metal bedpan. Patients were instructed to retain the fluid infused for as long as possible. The volume of fluid infused when a leak first occurred (easily audible) was recorded as the volume at first leak. Residual rectal volume was also calculated by measuring the volume of fluid in the commode at the end of the experiment (volume infused − volume in commode = residual rectal volume).

Perineal descent and pressure studies

Perineal descent was measured using a jig placed on the ischial tuberosities with a mobile rod to assess position of the anus at rest and after straining[4,5]. A soft rubber balloon attached to a fine tube was placed in the rectum. The maximal resting and squeeze pressures in the anal canal were recorded at 1 cm intervals from the anal verge using a closed water-filled balloon probe (diameter 6 mm) connected to a strain gauge amplifier and recorder. Three parameters of rectal sensation were measured using a rectal balloon which was inflated with increasing increments of air: first, transient sensation (threshold), second, constant feeling of rectal distension (constant), and finally the maximum amount of air tolerated below 400 ml (maximum tolerated volume). The recto-anal inhibitory reflex was studied, the maximum fall of pressure from baseline levels was measured as well as the duration of the reflex.

Rectal compliance (V/P) was assessed by a rectal balloon the lower part of which was stationed 6 cm above the anocutaneous junction. This balloon was connected via a three-way tap to an air filled pressure transducer. The balloon was first calibrated in air using 50 ml increments of air introduced into the balloon up to a maximum of 200 ml. The balloon was then placed in the rectum and 50 ml increments of air introduced into the balloon again to a maximum of 200 ml. Corresponding pressure changes were recorded using the transducer and the intrinsic pressure exerted by the balloon in air was subtracted from the sum of the pressure exerted by the rectal wall and the balloon. It was then possible to calculate the change in rectal volume for a given change in rectal pressure and this parameter was plotted.

Balloon proctography

The first 20 patients in this study underwent balloon proctography. In addition, four control individuals with no known gastrointestinal disease also agreed to be studied. With the patient in the left lateral position, a well lubricated balloon mounted on a soft catheter was introduced into the rectum. The balloon was filled with 100 ml of

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barium/water mixture. The patient was then placed over a radiolucent lavatory seat in the normal position for defaecation. A radio-opaque marker was placed over the pubis. A lateral pelvic radiograph was then taken to define the position of the balloon in the rectum at rest. A video-recording was taken during maximal pelvic floor contraction and then during attempted defaecation. From this recording it was possible to measure the degree of perineal descent in relation to the pubococcygeal line. The anorectal angles were also measured during these manoeuvres as described by Preston *et al.*[6]

Statistical methods

As the manometric data and results of the saline infusion tests were non-parametric, median values and ranges are quoted in the text. The Mann–Whitney *U* test was applied using a two-tailed *P* value for statistical analysis. Anorectal angles were normally distributed and were analysed by the Student's *t* test using means and standard deviations to describe the results in the text. Relationships between linear analogue score and results from saline infusion were analysed using the least squares regression analysis. Computation of compliance also was carried out using least square regression analysis.

Ethical

The study was approved by the Ethical Committee of the Central Birmingham Health Authority.

Results

Microbiological studies

No fluorescence under ultraviolet light was found in any patient or control individual. No ova, cysts, or parasites were found on microscopy from any individual. Perineal swabs identified one pruritic patient with a light growth of *Candida albicans* and another with a small inoculum of *Rhodotorula* sp.

Saline infusion test

The median volume of saline at which leakage first occurred in the pruritic group was 600 ml (220–1500 ml), compared with 1300 ml (550–1500 ml) in the controls ($P<0{\cdot}001$) (*Figure 1*). The residual rectal volume at the end of the test had a median value of 720 ml (300–1500 ml) in the pruritus patients and 1450 ml (500–1500 ml) in the controls ($P<0{\cdot}001$) (*Figure 1*). Analysis of these values in the patients with pruritus indicated no difference between those with anal disease and those without, 550 ml (220–1500 ml) and 600 ml (300–1500 ml) respectively for the volume at which leakage first occurred. There was, however, a significantly lower value for the volume at which leakage first occurred in patients with pruritus unaccompanied by co-existing anal disease, 600 ml (300–1500 ml) compared with controls ($P<0{\cdot}001$). In 13 consecutive patients with pruritus ani a record of severity of pruritus (as assessed with linear analogue score) was compared with the volume of saline at which leakage first occurred and the residual rectal volume. There was an inverse correlation between severity of pruritus and the result of the saline infusion test ($r=-0{\cdot}614$) $P<0{\cdot}02$ for volume at first leak and ($r=-0{\cdot}736$) $P<0{\cdot}01$ for residual rectal volume (*Figure 2*). In a small number of patients ($n=9$) the saline infusion test was repeated two months after the initial test. Severity of pruritic symptoms was also measured at this time on the linear analogue scale. The results of this are shown in *Table 1*. They show that any improvement in pruritic symptoms as assessed by linear

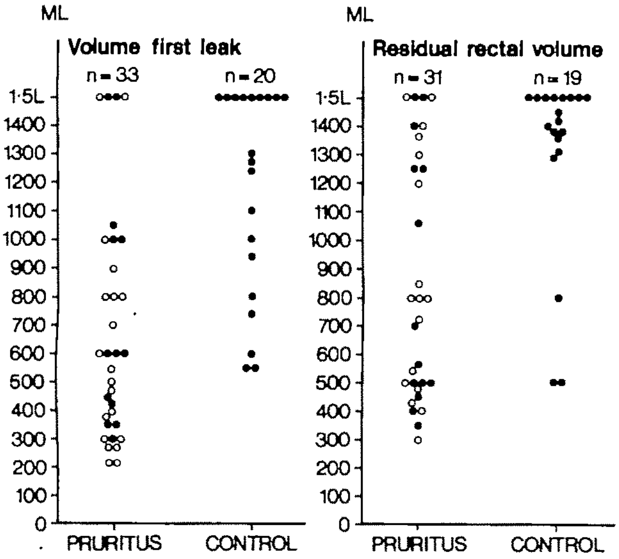

Figure 1 *Saline infusion test. Each point represents the result for an individual patient.* ○, *Co-existing anal disease;* ●, *no co-existing anal disease. Pruritus* versus *control: volume first leak,* $P<0{\cdot}001$; *residual rectal volume,* $P<0{\cdot}001$

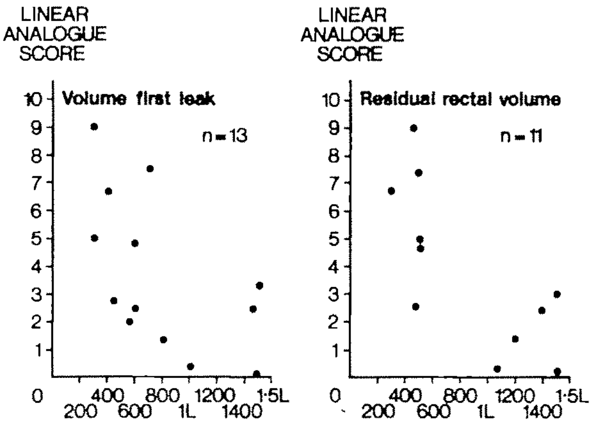

Figure 2 *Relationship of linear analogue score to results of saline infusion test. Volume first leak,* $r=-0{\cdot}614$, $P<0{\cdot}02$; *residual rectal volume,* $r=-0{\cdot}736$, $P<0{\cdot}01$

Table 1 *Comparison of saline infusion test and linear analogue scale of pruritus at repeated intervals in nine individuals*

	Initial test			Two months			
Patient	Linear analogue scale (1–10)	Volume first leak (ml)	Residual rectal volume (ml)	Linear analogue scale (1–10)	Volume first leak (ml)	Residual rectal volume (ml)	Change in clinical state of patients
1	6·7	400	300	5·0	600	500	Improved
2	9·0	300	450	4·1	450	300	Improved
3	4·8	600	500	6·6	550	750	Worse
4	0·1	1500	1500	0·3	1500	1450	No change
5	3·3	1500	1500	3·5	800	700	No change
6	0·4	1000	1060	0·4	1300	1500	No change
7	5·0	300	500	3·5	750	1050	Improved
8	4·8	800	—	1·0	500	—	Improved
9	2·5	600	480	4·0	500	1100	Worse

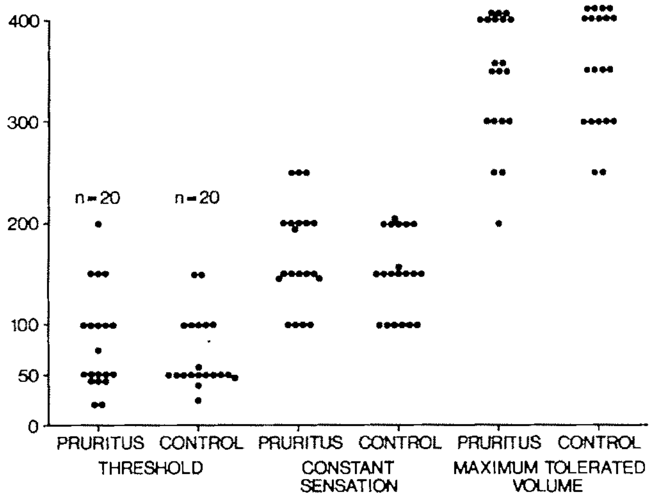

Figure 3 *Results of balloon distension of the rectum with air. The threshold, constant and maximum tolerated volumes are plotted for each patient. Each point represents one patient*

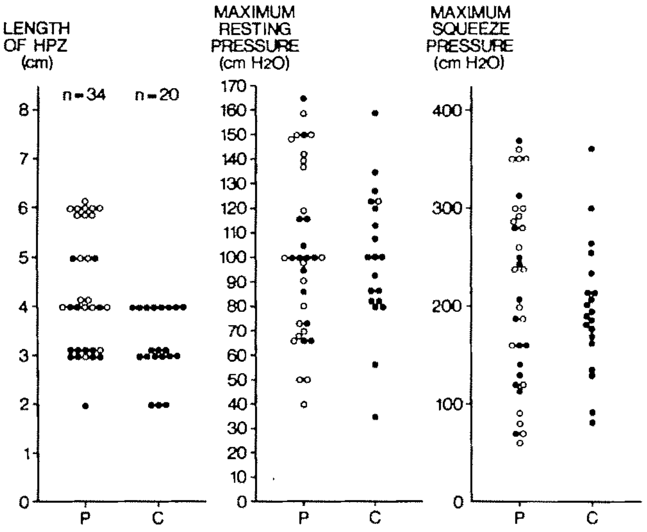

Figure 4 *Results of manometric tests of anal sphincter function. HPZ, high pressure zone*

analogue scale was accompanied by a higher volume at first leakage on the saline infusion test.

Perineal descent and manometric studies

Perineal descent during straining was 1·5 cm (0·3–4·0 cm) in patients with pruritus compared with 1·3 cm (0·8–2·3 cm) in the controls. Only four individuals had values which lay above the upper limit of normal of 2·5 cm[4,5] and all were in the pruritic group.

None of the parameters of rectal sensation differed between the groups (*Figure 3*). The median maximum tolerated volume was 350 ml (200–400 ml) in the pruritic group compared with 350 ml (250–400 ml) in the controls.

The median length of the high pressure zone in the pruritus group was 4 cm (2–8 cm) compared with 3 cm (2–4 cm) in the controls (n.s.). The median maximal anal resting pressure was 5·2100 cmH_2O (40–164 cmH_2O) in the patients compared with 100 cmH_2O (35–160 cmH_2O) in the controls (n.s.). The maximum squeeze pressure was 239 cmH_2O (60–360 cmH_2O) in the patients compared with 192 cmH_2O (80–360 cmH_2O) in the controls (n.s.) (*Figure 4*).

The percentage fall in the resting anal pressure after inflating a balloon in the rectum with 50 ml of air was 47 per cent in patients compared with 40 per cent in controls (n.s.) (*Figure 5*). However, when the pruritic patients with no co-existing anal disease were compared with the controls, there was a significantly greater fall in pressure (57 per cent) among these pruritic patients ($P < 0{\cdot}05$). No difference was observed between the pruritic patients with co-existing anal disease and control individuals. The duration of the reflex was shorter in patients with pruritus (15 s) compared with the controls (20 s) (n.s.). Rectal compliance was similar in the pruritic and control group being 5·2 ml/cmH_2O in the pruritics and 5·9 ml/cmH_2O in the control patients.

Balloon proctography

The anorectal angles for the pruritic group and the control subjects are shown in *Table 2*. There was no statistical difference between the groups. However, the anorectal angle increased in four of the patients with pruritus during pelvic floor contraction whereas the angle decreased in the controls. Furthermore, the anorectal angle closed in two of the pruritic patients when asked to expel the balloon and four pruritus patients were unable to expel the balloon (20 per cent).

Discussion

Both the pruritic and the control group in this study were well matched for age and sex. This is important as anal pressures are known to be lower in the elderly subjects when compared with younger persons[7]. Furthermore, anal pressures in women, particularly those who have had several children, tend to be lower compared with men[8,9]. Despite careful screening, we were unable to find more than two patients with a fungal skin colonization and even these subjects had only a small inoculum. The perianal skin was examined under an ultraviolet light for the presence of *C. minutissimum* but no such organisms were found. *C. minutissimum* represents an uncommon cause of pruritus ani[10].

The results of the saline infusion test indicated that patients

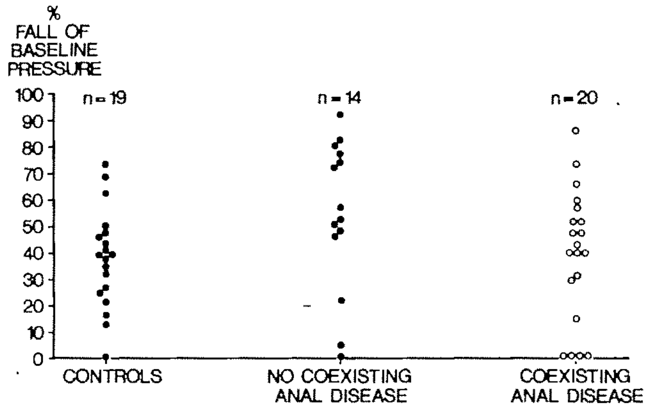

Figure 5 *Results of distending of the rectum with a balloon (50 ml air). Percentage fall baseline pressure is shown. No co-existing anal disease versus controls,* $P < 0{\cdot}05$

Table 2 *Anorectal angles as measured by balloon proctography*

	Angles		
	At rest	Squeeze	Expel
Pruritus ($n = 20$)			
Mean	107	95	127
Range	45–130	70–125	65–150
s.d.	±22	±16	±23
Control ($n = 4$)			
Mean	111	87·5	135
Range	70–140	60–150	100–165
s.d.	±33	±43	±29

with pruritus ani leak liquids more readily than the control group. It is not possible from this study to know whether the leakage caused the pruritus ani or *vice versa*. It seems more likely that the leakage was the predisposing cause for pruritus. But it was not possible to demonstrate that the leakage of saline was the underlying defect as pruritus symptoms did not occur independently of increased leak in pruritic patients. Repeat saline infusion tests at two monthly intervals in a small number of patients reveal a tendency for symptoms to vary with time but to correlate with the results of the saline infusion test.

In a previous study[11] it was shown that haemorrhoids occurred more commonly in patients with pruritus than in the normal population and that itching was reduced by haemorrhoidectomy or by rubber band ligation. It is possible that in our study co-existing anal disease was the cause of the increased leakage found on the saline infusion test in those patients with co-existing pathology. However, our results suggest that co-existing anal disease is not the sole cause of increased leakage of saline because the results of saline infusion in patients with pruritus but no other anal disease, did not differ from those with anal disease. On the other hand there was a significantly decreased volume at first leak in patients with pruritus but no co-existing anal disease compared with controls with no co-existing anal disease. This further supports the view that the presence of co-existing anal disease is unlikely to be the cause of an increased leakage of fluids across the sphincter in pruritic patients. Our study shows a greater fall in anal pressure after rectal distension in patients with pruritus ani but no co-existing disease compared with normal controls. This finding has been reported previously[12] and may account for the increased leakage in these patients. It is, therefore, possible to hypothesize that pruritus ani is caused by an increased leakage of fluid through the anal sphincter and this leakage is in turn caused by the presence of either co-existing anal disease or an exaggerated recto-anal inhibitory reflex in those patients with pruritus ani alone.

The high pressure zone was longer in patients with pruritus ani than in controls but the difference was not statistically significant. Likewise maximum squeeze pressures were higher in those with pruritus ani compared with controls but again differences were not statistically significant. It is known that patients with haemorrhoids have increased internal sphincter activity[13–15] and in some external sphincter hypertrophy develops[16] which may account for the slightly longer high pressure zone in the pruritic group. It is also conceivable that some anal sphincter hypertrophy may have occurred in response to the irritant effect of faecal soiling. Rectal compliance was similar in the pruritic and control group of patients suggesting that decreased rectal compliance in pruritic patients was not a predisposing factor to increased leakage.

This study shows a marked increase in leakage through the anal sphincter in patients with pruritus ani compared with control individuals. It seems possible that such increased leakage is caused by either the presence of co-existing anal disease or else an exaggerated recto-anal inhibitory reflex.

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Paper accepted 13 February 1987

Br. J. Surg. 1987, Vol. 74, July,
580–581

Mechanical bowel preparation for colonic resection and anastomosis

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In a series of 72 consecutive elective and emergency colectomies with primary anastomosis, all pre- and perioperative mechanical preparation of the bowel was omitted and the patient covered only by a single peroperative intravenous dose of cefuroxime and metronidazole. No anastomotic dehiscence was clinically apparent and wound infection was noted in only 8·3 per cent of patients.

Keywords: Colectomy, bowel preparation, wound infection

Wound sepsis following colorectal surgery is related to the perioperative contamination of the wound with faecal organisms[1]. Traditionally, 'bowel preparation' has been used to reduce faecal mass and also bacterial counts. Several trials have shown that wound sepsis rates can be reduced by combining a pre-operative regimen of mechanical bowel preparation with a system of 'bowel sterilization' using a pre-operative course of oral intestinal antiseptic[2] or oral antibiotics[3]. Although most surgeons consider mechanical bowel preparation to be essential[4–6], it is now recognized that the systemic administration of appropriate antibiotic is effective in reducing wound sepsis by saturating the tissue at the time of contamination[7–9].

While many seek improved methods of mechanical bowel preparation to obtain a 'clean' colon, we question whether it is necessary provided antibiotics are used appropriately. This preliminary study describes the results of colonic resection with primary anastomosis performed on 'unprepared' bowel with the administration of only single dose peroperative broad-spectrum antibiotics.

Patients and methods

A consecutive series of 72 patients (mean age 70 years, range 36–103 years) was studied. All the elective patients were admitted the day before operation and received a normal ward diet. In no case was the bowel prepared pre-operatively with purgative, enema, oral intestinal antiseptic or antibiotic. Patients were excluded if bowel preparation had been carried out for colonoscopy or barium enema examination within 2 weeks before admission. Emergency resection and anastomosis were carried out in 19 cases: for obstruction in 14, perforation in 2, abscess in 1, bleeding in 1 and acute diverticulitis in 1 case. There were a further nine patients during the period of the study who had established peritonitis and in whom anastomosis was deemed inadvisable. Hartmann's procedure was carried out in these nine cases.

Twenty-four patients had an anastomosis carried out in the sigmoid or descending colon. Twenty-two had anterior resection of the rectum and 26 patients underwent right hemicolectomy (*Table 1*). Surgery was performed for malignant disease in 63 and for diverticular disease in 9 patients.

Laparotomy was carried out through a mid-line incision. Wound towels or protectors were not used. The bowel was divided between occlusion clamps only and the resection lines were cleaned with Hibitane swabs. Bowel continuity was restored with a single layer anastomosis of interrupted 2/0 Nuralon using an inverting technique fully described previously[10,11]. The integrity of the anastomosis was tested by manually raising the intraluminal pressure across the suture line and was considered satisfactory by the absence of mucosal eversion or leakage of air or faeces. Cefuroxime (750 mg) and metronidazole (500 mg) were administered intravenously at the start of the operation after induction of anaesthesia. Antibiotics were not continued postoperatively. The abdomen was closed by mass suture (no. 1 monofilament nylon) after copious saline lavage. Gloves were not changed. The skin was approximated by a subcuticular Prolene suture which was removed on the sixth day. Drains and colostomies were never used. Nasogastric suction was not used routinely and free oral fluids were encouraged within the first 24 hours. A low anterior resection was defined as an anastomosis below the peritoneal reflection. Wounds were inspected daily until discharge from hospital and thereafter at 3 and 6 weeks. Sepsis was defined as the discharge of pus or serum at any time from the wound within 6 weeks. Anastomotic dehiscence was diagnosed on clinical grounds alone.

Results

Wound infection occurred in six patients (8·3 per cent) (*Table 2*). Three wound infections occurred in the 53 elective cases (5·7 per cent), and 3 in the 19 emergency cases (16 per cent), 2 of whom were among the 9 patients (22 per cent) who had surgery for diverticular disease. Only one patient required postoperative nasogastric suction for gastric dilatation. The mean duration of hospital stay for all patients was 12 days. No patient developed

Table 1 *Relationship between type of resection and wound infection in 72 patients undergoing elective or emergency large bowel resection*

Type of resection	*n*	Elective	Emergency	Wound infection
Sigmoid and descending colon	24	18	6	4 (emergency 2, elective 2)
Anterior resection				
High	12	9	3	1 (elective)
Low	10	7	3	—
Right hemicolectomy	26	19	7	1 (emergency)

Table 2 *Wound infections following large bowel resection*

Patient	Operation	Disease	Wound
A	Sigmoid resection (emergency)	Diverticulitis	Serous discharge day 5
B	Right hemicolectomy (emergency)	Perforated caecal diverticulum	Purulent discharge day 21
C	Sigmoid resection (emergency)	Obstructed sigmoid carcinoma	Serous discharge day 12
D	Left hemicolectomy (elective)	Fixed descending colon carcinoma	Purulent discharge day 4
E	Left hemicolectomy (elective)	Recurrent fixed descending colon carcinoma	Purulent discharge day 9
F	Anterior resection (elective)	Carcinoma with sigmoid diverticular disease	Serous discharge day 14

clinical evidence of anastomotic leakage. Two deaths occurred in the immediate postoperative period; one from myocardial infarction (first day) and one from cerebrovascular accident (fourth day). There was no evidence of anastomotic leakage or wound infection at post mortem in either case.

Discussion

The search continues for the 'best' method of mechanical bowel preparation for colonic surgery. This has included oral aperients, rectal enemas and colonic wash-outs, elemental diets and whole gut irrigation[5,6,12]. Mechanical bowel preparation alone has not convincingly been shown to decrease the concentration of faecal organisms within the bowel, wound sepsis rates or the incidence of anastomotic dehiscence[5,13–15]. Mechanical methods of bowel preparation do have a morbidity, including perforation. Whole gut irrigation carried out on the day before operation is exhausting and distressing to patients, many of whom are elderly, and may cause electrolyte disturbance[16]. We also consider that bowel preparation simply converts solid, manageable faeces into an uncontrollable liquid contaminant. Peroperative intracolonic irrigation[17] carries this same disadvantage and considerably prolongs operation time. Although faecal loading and spillage have been reported as contributing to anastomotic leakage[4], the incidence of anastomotic leakage is certainly related more to surgical technique[18].

Wound infection is related to the incidence of inoculation of organisms into the wound at the time of surgery[1,19,20]. Although oral non-absorbable antibiotics may reduce the incidence of wound infection, they must be administered for up to 5 days pre-operatively and carry a risk of resistant superinfection[8,14]. Systemic administration of antibiotic around the time of operation offers a greater reduction in wound sepsis[7–9]. We did not worry about leakage of manageable faeces as these were removed manually and by copious wash-outs of saline. The systemic effects were minimized by tissue saturation and high circulating levels of intravenously administered peroperative antibiotics.

Six cases of wound infection were recorded. We emphasize that sepsis was sought by daily inspection until discharge then routinely at 3 and 6 weeks postoperatively, as the late appearance of wound infection is well described[21]. It is noted that in elective resection and anastomosis, the wound infection rate, at 5·7 per cent, is considerably less than the 16 per cent in emergency cases. In any event, most of the documented methods of mechanical preparation and pre-operative bowel 'sterilization' are inappropriate in the emergency situation. The incidence of wound sepsis in our series, particularly in elective cases where 'bowel preparation' was not used, compares very favourably with all other published data[22,23] with the exception of the excellent results from Aberdeen[24].

We conclude that in colonic resection and anastomosis, pre-operative 'bowel preparation' using mechanical methods or oral antibiotic is unnecessary provided that appropriate antibiotic is administered intravenously during the operative period.

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Paper accepted 6 February 1987

Br. J. Surg. 1987, Vol. 74, July,
582–585

Diseases of the breast in Nigeria

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For the purpose of defining the distribution of breast diseases in Nigeria, a review of 671 cases seen in Ife over a 10 year period was undertaken. Twenty-six (3·9 per cent) of the patients were males. The frequency of breast diseases in this population was fibro-adenoma, 48 per cent; carcinoma, 21 per cent; breast abscess, 8·6 per cent; fibrocystic disease, 5·5 per cent; sclerosing adenosis, 5·4 per cent and gynaecomastia, 2·7 per cent. The other breast lesions were the same type of disease as documented in white patients. The most striking difference was the relatively high incidence of fibro-adenoma, especially in nulliparous adolescent females, while carcinoma and fibrocystic disease were fewer than expected. Breast carcinoma presented a decade earlier in Nigerian women and was usually advanced at presentation and of aggressive histological type. Of the breast carcinomas, 4·3 per cent were associated with pregnancy.

Keywords: Breast diseases, breast cancer, fibro-adenoma

Although cancer of the breast has been described for centuries, the relative lack of literature on its incidence in Africa is of great concern to all clinicians practising in this area. It is the purpose of this study to analyse the distribution pattern of breast diseases with histological confirmation seen over a period of 10 years in Ife University Teaching Hospitals Complex, Ile-Ife, Nigeria.

Materials and methods

During a 10 year period, 1977 to June 1986, 671 cases with biopsy proven breast lesions were seen in the Departments of Surgery and Pathology of Ife University Teaching Hospitals Complex, Ile-Ife, and form the basis of this study. Between 1977 and 1981, an average of 40 cases were seen annually. There was a steady rise in the number of cases from 69 in 1982 to 112 in 1985. The surge in the number of cases seen in 1984–1986 was associated with the breast cancer campaign launched in 1984 by the Nigerian Cancer Society. The case notes of the patients were reviewed with special attention to sex, age at time of diagnosis, size and location of the lesion, stage of breast carcinoma and other associated malignancies. It is our intention to study only the distribution of the various breast diseases without describing subsequent management.

Results

Pathological distribution

Of 671 patients, 532 (79 per cent) had benign breast lesions and 139 (21 per cent) had breast cancer (*Table 1*). Patients with benign breast disease were thus approximately four times more numerous than those with breast cancer. Fibro-adenoma was the most common lesion of the breast accounting for 48 per cent of the entire lesions and 61 per cent of benign breast disease. The descending order of frequency of the lesions was fibro-adenoma, 48 per cent; carcinoma, 20·6 per cent; pyogenic breast abscess, 8·6 per cent; fibrocystic disease, 5·5 per cent; sclerosing adenosis, 5·4 per cent; and gynaecomastia, 2·7 per cent. The other major lesions included cystosarcoma phyllodes, intraductal papilloma, lactating adenoma and lipoma. A single case of tuberculous mastitis was seen.

Sex distribution

Of the 671 patients, 645 (96·1 per cent) were females and 26 (3·9 per cent) were males giving a female:male ratio of 25:1.

Benign breast lesions

As we earlier reported[1], the mean age for all benign lesions was 25 years with the peak age between 18 and 35 years. The age range for fibro-adenoma was 13–48 years with a peak from 16 to 25 years and a mean age of 21 years. The mean age for fibrocystic disease was 37 years with a peak age incidence of 30–45 years.

With the exception of three of eight patients with intraductal papilloma presenting with nipple discharge, all patients with benign breast lesions presented with breast masses. The size of the lesions varied from 5 mm to 19 cm. The largest mass was cystosarcoma phyllodes. The intramammary location of the lesions showed that 62 per cent of all benign lesions and 69 per cent of fibro-adenomas were found in the two lateral quadrants of the breast respectively. With regard to laterality, 48·5 per cent of fibro-adenomas occurred in the right breast, 35·3 per cent in the left and 16·2 per cent were bilateral. In 14 per cent of all benign disease, multiple lesions were present in one or both breasts at operation. Fibro-adenoma was frequently associated with other benign tumours especially sclerosing adenosis. The highest number of fibro-adenomata removed from both breasts at one operation was 48, in a 23-year-old nulliparous female.

Table 1 *Pathological distribution of diseases of the breast in 671 patients*

Pathology	Number	Percentage of all lesions (671)	Percentage of benign lesions (532)
Carcinoma	138	20·6	—
Fibro-adenoma	324	48·3	60·9
Breast abscess	58	8·6	10·9
Fibrocystic disease	37	5·5	7·0
Sclerosing adenosis	36	5·4	6·8
Gynaecomastia	18	2·7	3·4
Cystosarcoma phyllodes	9	1·3	1·7
Intraductal papilloma	8	1·2	1·5
Lactating adenoma	8	1·2	1·5
Lipoma	7	1·0	1·3
Epithelial hyperplasia	6	0·9	1·1
Duct ectasia	5	0·7	0·9
Fat necrosis	4	0·6	0·8
Neurofibroma	3	0·5	0·6
Granuloma	2	0·3	0·4
Galactocele	2	0·3	0·4
Duct papillomatosis	2	0·3	0·4
Dematofibroma	2	0·3	0·4
Non-Hodgkin's lymphoma	1	0·2	—
Tuberculous mastitis	1	0·2	0·2
Total	671	100	100

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Of the other major benign breast lesions, pyogenic breast abscess accounted for 58 cases (10·9 per cent) and was in all cases related to lactation. The other benign breast lesions associated with pregnancy and lactation were lactating adenoma (eight cases), epithelial hyperplasia with hypertrophy (six cases) and galactocele (two cases). *Figure 1* illustrates a case of epithelial hyperplasia with hypertrophy in a 25-year-old woman who was referred by her obstetrician at 30 weeks gestation with bilateral breast masses, hypertrophy, oedema and peau d'orange which raised the question of malignancy. Bilateral breast biopsies revealed epithelial hyperplasia and the patient was reassured that there was no evidence of malignancy. The breasts returned to normal post partum and she was able to breast feed her baby.

Malignant breast lesions

Of 671 patients, 139 had breast cancer. The malignant lesions comprised 138 carcinomas (99·3 per cent) and a case of non-Hodgkin's lymphoma found in the right breast of an 8-year-old boy. Only four of the cases were seen in men. *Table 2* shows the histological types of the malignant diseases. Nearly 82 per cent of the cell types represented the unfavourable and highly malignant tumours comprising poorly differentiated adenocarcinoma, infiltrating ductal carcinoma, anaplastic carcinoma and inflammatory carcinoma. The peak age incidence for breast carcinoma was 40–49 years with a mean of 42 years and a range of 20–81 years (*Table 3*) and 52·5 per cent of the lesions occurred in the left breast and 47·5 per cent in the right. Three patients had synchronous carcinoma in both breasts at the time of diagnosis. Only 26 patients (18·8 per cent) had stage I or II disease on presentation. *Figure 2* illustrates the classical mode of presentation of breast carcinoma in Nigeria where most patients waited until their lesions were big, foul smelling or ulcerated before seeking medical treatment. Two patients had synchronous contralateral deltoid sarcoma and metachronous hepatoma respectively.

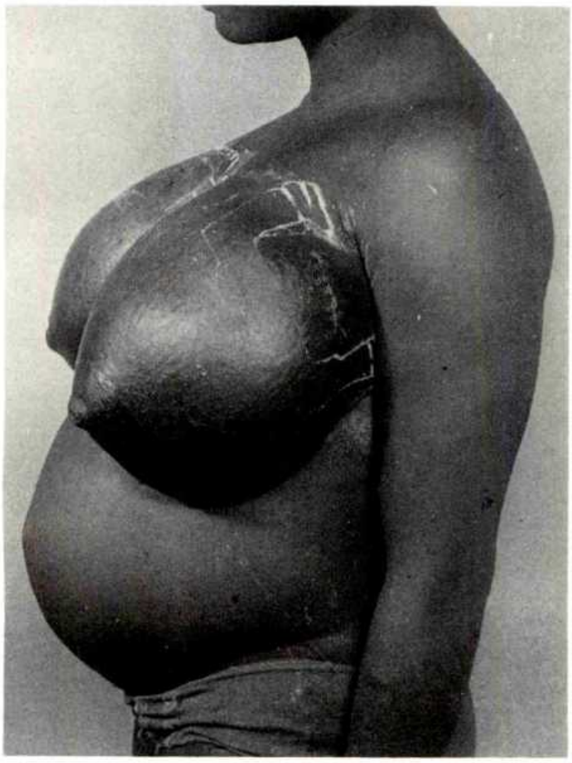

Figure 1 *Twenty-five-year-old pregnant woman with bilateral breast masses, massive swelling, oedema and peau d'orange. Bilateral breast biopsies showed epithelial hyperplasia*

Table 2 *Histological distribution of malignant breast disease*

Histological type	Number	Percentage
Poorly differentiated adenocarcinoma	47	33·8
Infiltrating ductal carcinoma	42	30·2
Anaplastic carcinoma	13	9·4
Inflammatory carcinoma	11	7·9
Scirrhous carcinoma	8	5·7
Medullary carcinoma	4	2·9
Paget's disease	3	2·2
Intraductal carcinoma	3	2·2
Papillary carcinoma	3	2·2
Comedocarcinoma	2	1·4
Lobular carcinoma	1	0·7
Carcinosarcoma	1	0·7
Non-Hodgkin's lymphoma	1	0·7
Total	139	100

Table 3 *Age specific incidence of malignant breast disease*

Age (years)	Number	Percentage
0–9	1	0·7
20–29	13	9·3
30–39	28	20·1
40–49	38	27·0
50–59	32	23·0
60–69	23	17·0
70–79	3	2·2
80–89	1	0·7
Total	139	100

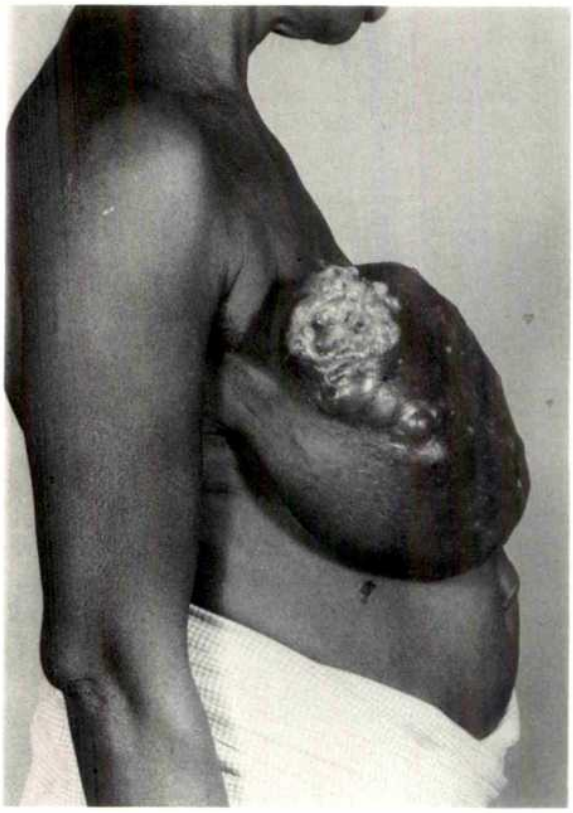

Figure 2 *Ulcerating advanced carcinoma of right breast in a 48-year-old woman*

Of the 138 patients with breast carcinoma, 6 (4·3 per cent) were pregnant at the time of diagnosis of their disease. The mean age of the six patients was 28·8 years (a range of 26–33 years) and a mean duration of pregnancy at presentation with breast cancer was 22 weeks (a range of 12–36 weeks). In three instances, the lesion was inflammatory carcinoma while the others were two cases of poorly differentiated adenocarcinoma and a case of infiltrating ductal carcinoma.

Male breast lesions

There were 26 men among the 671 patients. Their lesions comprised 18 cases of gynaecomastia, 3 of fibro-adenoma, a case of lipoma, 3 of carcinoma and a case of non-Hodgkin's lymphoma. The mean age of the 18 patients with gynaecomastia was 20·8 years. Eight of the cases were bilateral, six occurred in the right breast and four in the left. All the patients with fibro-adenoma were 21 years of age and the only case of lipoma occurred in a 40-year-old man. The mean age of patients with breast carcinoma was 56·7 years (range 55–60 years).

Discussion

While clinical attention is rightly focused on carcinoma as the most important disease of the breast, benign lesions are, in fact, much more frequent than malignant ones as demonstrated by this study which shows that benign breast disease is four times as common as cancer. The true incidence of breast diseases in the Nigerian population is unknown because the source of our data is a University Teaching Hospital. Data obtained from this type of study is influenced by many factors which include socio-economic status and level of awareness of the population, availability of medical facilities, hospital location and admission policies, patient selection and referral system. Incidence rates of diseases are usually difficult to calculate in Nigeria because demographic data are either not available or inaccurate. It is our view that the incidence of breast diseases in this population is underestimated.

An analysis of our data indicates that fibro-adenoma is the most common breast lesion in Nigeria. This finding reinforces earlier reports from America[2–4], Africa[1,5,6] and West Indies[7] indicating a relatively higher incidence of fibro-adenoma among black patients compared to whites. These reports show that fibro-adenoma occurs at an earlier age in blacks and is more common than carcinoma in contrast to studies[8,9] in white populations showing the order of frequency of breast diseases as fibrocystic disease, cancer and fibro-adenoma. The early peak age incidence of 16–25 years with a mean of 21 years for fibro-adenoma is due to the high incidence of fibro-adenoma in nulliparous adolescent Nigerian females.

The 5·5 per cent incidence of fibrocystic disease in this series is low but similar to the finding in East Africa[6]. It may be that the disease is less common in African women than in whites where reports[8,9] show a relatively high incidence of fibrocystic disease but the incidence of fibrocystic disease in Africa may be due to the unwillingness to present at hospitals with a breast lump unless it is large or advancing. The low incidence of fibrocystic disease relative to fibro-adenoma in this population may be due to the fact that fibro-adenoma occurs in younger patients who are educated, and have access to health education on breast examination and therefore know the importance of the early detection of breast cancer.

Inflammatory lesion is one of the common benign breast lesions in this series. This comprised 58 cases of pyogenic breast abscess and a case of tuberculous mastitis. Pyogenic breast abscess is related to breast feeding which is commonly practised by Nigerian women. We suspect that the true incidence of the lesion is higher than our data indicate because many patients have incision and drainage of their abscesses in the surgical emergency room without the benefit of biopsy of their lesions for histological examination. It is hoped that with effective use of antibiotics, there would be a decline in the incidence of this lesion. The unexpected low incidence of tuberculous mastitis in a country where tuberculosis is prevalent is surprising. However, this finding is similar to reports from other parts of Africa[5,6,10] and the Far East[11,12] where tuberculosis is common. Understandably, the incidence of the lesion in industrialized Western nations where tuberculosis is rapidly disappearing, is very low[3,8,13]. The relatively low incidence of turberculous mastitis worldwide has been attributed to inexplicable immunity of the breast tissue to tuberculosis[12].

Breast carcinoma accounts for 21 per cent of all breast lesions in this study. The mean age of 42 years (range of 20–81 years) compares favourably with the reports from Ibadan[14] and Uganda[6]. The onset of the disease is at least 10 years earlier in the African population than whites[8,9,15]. Eighty per cent of our patients were under 60 years with 57 per cent premenopausal when the diagnosis of their disease was made. The data from the Ibadan cancer registry (1960–1980) reported by Abioye[16] in 1981 showed that breast carcinoma comprised 11·2 per cent of all female tumours and was the second most common cancer after carcinoma of the cervix (19·9 per cent). These data are similar to the report from Uganda[6] showing that breast carcinoma accounted for 9·3 per cent of all female cancer and was the second most common tumour after carcinoma of the cervix (22·3 per cent). All these reports point to the fact that breast cancer is much less common in black women than whites.

Of great concern is the observation that 81 per cent of the patients with breast carcinoma presented with advanced disease (stages III and IV), nearly all of the tumours were of the highly malignant cell type with poor prognosis. These findings complement the earlier reports from Africa[6,14]. It is disappointing to note that the practice of not subjecting all excised breast masses in young women suspected of having fibro-adenoma to histological examination is common in general hospitals and private clinics in Nigeria. This series includes one patient whose 'fibro-adenoma' was not examined histologically until she presented 6 months later with advanced breast cancer and review showed ductal carcinoma in the original specimen. Recent reports[17,18] indicate that the incidence of carcinoma in fibro-adenoma may not be as rare as was earlier thought. The 4·3 per cent incidence of breast carcinoma associated with pregnancy is similar to the 1·5–4 per cent reported in white patients[19,20]. Unfortunately the tumours in our patients were advanced and highly malignant at the time of presentation.

Gynaecomastia is the most common breast disease found in men in this study. The 2 per cent incidence of carcinoma of the breast in men out of the 138 breast carcinomas in this series is similar to the finding in Ibadan[16] and contrasts with the 12 per cent incidence reported from Uganda[6]. The incidence of the disease in Nigerian male patients compares well with the 1 per cent incidence in white males[13]. The mean age of male patients with breast carcinoma was at least a decade higher than that in women. It is surprising that there was no case of Burkitt's lymphoma of the breast in our patients. Reports from Ibadan[21,22] and Uganda[23] show that Burkitt's lymphoma can present as unilateral or bilateral swelling of the breast in women of child-bearing age.

In conclusion, this study shows that benign breast disease presents four times as often as carcinoma of the breast in Nigerian women. An analysis of our data suggests that fibro-adenoma is more common while fibrocystic disease and breast cancer present less often in black than white patients. The fact that breast carcinoma is seen at an advanced stage in a majority of the patients makes the prognosis less favourable. It is suggested that health education on breast examination and early detection of breast disease is as important in Africa as it is elsewhere.

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Paper accepted 14 February 1987

Case reports

Br. J. Surg. 1987, Vol. 74, July, 585–586

Gigantomastia in pregnancy

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Breast enlargement in pregnancy is a physiological response to hormonal stimulation in preparation for lactation after parturition. This natural phenomenon in rare instances becomes grossly exaggerated resulting in the unusual development of crippling gigantomastia.

Case report

A 28-year-old woman presented at 19 weeks in her third pregnancy complaining of a marked increase in her breast size associated with severe local tenderness, discomfort and backache. She reported that her brassiere size had increased from 36C to 50D. Ten years previously her first pregnancy had ended in a miscarriage at 14 weeks and her second pregnancy 2 years later was uneventful and accompanied by normal breast enlargement (brassiere size 38B) with lactation which continued for 4 months and was followed by spontaneous regression in size. A year before her present complaint she presented with multiple bilateral breast masses which after excision biopsy had the histological features of fibro-adenomata.

On this admission both breasts showed symmetrically gross enlargement with hyperaemia, thickened oedematous skin and tenderness to palpation, with generalized nodularity. There was bilateral enlargement of axillary breast tissue. Assays of prolactin, oestrone, oestradiol, progesterone, human placental lactogen, β subunit human chorionic gonadotrophin, human growth hormone, thyrotrophin, free thyroxine and urinary free cortisol were all within normal limits for 19 weeks gestation. These investigations were repeated on four occasions over the ensuing 10 weeks and remained normal for the time of pregnancy.

Bromocriptine 2·5 mg twice daily was commenced and 2 weeks later the patient reported a decreased tension in the breasts with some symptomatic relief. The serum prolactin decreased and remained at non-pregnant levels. There was no further change in the breasts themselves but a slow and steady increase in the axillary breast tissue which became progressively more painful necessitating admission to hospital at 30 weeks (*Figure 1*). Premature labour at 33 weeks was followed with delivery of a normal infant by Caesarean section.

She was placed on the injectable contraceptive Depo-Provera (medroxyprogesterone acetate) and over the ensuing 3 months her breasts underwent partial, but not complete, regression. She was therefore submitted to bilateral total mastectomy with insertion of subpectoral prostheses.

The left breast weighed 1800 g and the right 1750 g. The cut surfaces showed numerous well circumscribed soft brown nodules of varying

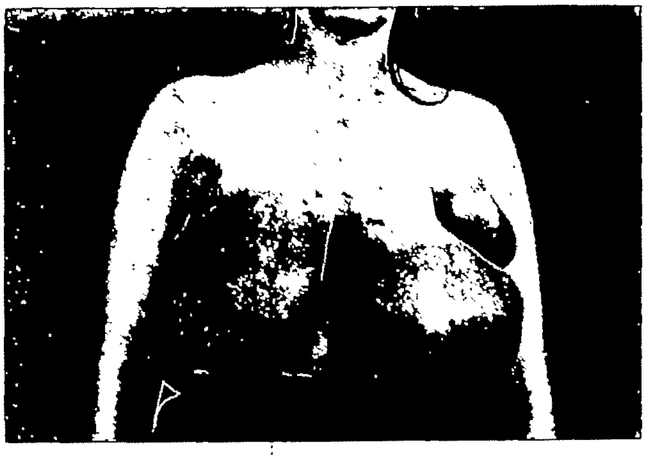

Figure 1 *The appearance of the breasts and accessory tissue at 30 weeks gestation*

0007–1323/87/070585–02$3.00

sizes, up to 6 cm in greatest diameter which were confirmed as fibro-adenomata. The intervening tissue consisted of extensive collagenous stroma within which were enlarged by atrophying lobules containing some residual secretory activity.

Discussion

Massive breast enlargement in gravid women is rare. In 1917 Deaver and McFarland analysed 240 cases of mammary hypertrophy of which 29 were probably true gigantomastia in pregnancy[1]. Levison reported two cases of his own in 1960 and reviewed the literature adding a further six isolated reports[2]. Since 1960 there have been a further 11 case reports[3–11] bringing the total number of reported cases, with our own, to 50.

The cause of this rare clinical entity remains obscure and open to speculation. All but two cases appeared at the end of the first trimester. Studies of various endocrinological parameters have thus far revealed no distinct hormonal cause[2]. An isolated report showed pathologically high serum prolactin levels[10], but we did not find this. The suggestion of target organ hypersensitivity[2] or an increased number of receptors[7] fails to explain the primary presentation in multigravid patients. The histological changes reported are essentially similar: there is massive hypertrophy of periductal and periacinal supporting tissue[2]. Marked oedema and dilatation of intralobular spaces is apparent. Multiple fibro-adenomata have been reported in three cases[2].

Numerous and varied forms of therapy have been tried in the past without success. These have included testosterone[2,6], stilboestrol[2,4], progesterone[9] and hydrocortisone[2]. Some response (as in our case) has been reported in three cases using bromocriptine[7,8,11] and a single case partially responded to the oral progesterone norethisterone[2].

Post-partum regression usually occurs[2], but this is not always the case[3,4,6,9,10]. Surgery has been necessary both in the pre- and post-partum states for mechanical reasons and for circulatory impairment which resulted in ulceration and sloughing[2]. As the condition is likely to recur in following pregnancies total mastectomy is usually preferred to breast reduction. Little progress has been made in the understanding and management of this rare and disfiguring condition.

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Paper accepted 26 January 1987

Br. J. Surg. 1987, Vol. 74, July, 586–587

Fatal hyperlipaemia in a case of metastatic breast cancer treated by tamoxifen

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The nonsteroidal oestrogen antagonist, tamoxifen, has a weak intrinsic oestrogenic activity on protein metabolism. Rossner and Wallgren[1] reported on the variations in plasma lipoprotein composition produced by tamoxifen therapy, and Brun *et al.*[2] reported a case with severe hyperlipaemia during tamoxifen therapy. They were not fatal. We report a case of fatal hyperlipaemia complicated by hepatic failure in association with tamoxifen therapy.

Case report

A 36-year-old woman had an extended radical mastectomy for breast cancer in September 1981. This was followed by daily oral administration of Tegafur (800 mg) and cyclophosphamide (100 mg), and weekly intravenous mitomycin (10 mg) for 5 weeks. From October 1983 daily tamoxifen (20 mg) was given orally. In December 1983 multiple metastases in both lungs were noted. Serum triglyceride and uric acid were slightly increased but the other laboratory data showed no abnormality. Daily tamoxifen (20 mg) and Tegafur (600 mg) were prescribed and she had a bilateral oophorectomy. One month later adriamycin (20 mg) and cyclophosphamide (500 mg) were given under the hypertensive condition induced by angiotensin II[3]. After 13 weeks the metastatic lesions in the lungs partially responded. In April 1984 hepatomegaly, splenomegaly and pancreatic enlargement were noted. The serum was grossly lipaemic. The laboratory data showed elevation of triglyceride level to 3673 mg/dl, cholesterol 301 mg/dl, phospholipid 593 mg/dl, lactate dehydrogenase 2754 units/l, total bilirubin 1·39 mg/dl, serum amylase 348 units/l, blood urea nitrogen 53 mg/dl and uric acid 31·9 mg/dl. The platelet count was $10{\cdot}9 \times 10^4\ \text{mm}^{-3}$. Ultracentrifugal analysis of lipoprotein revealed an elevation of low- and very low-density lipoprotein. Lipoprotein lipase and hepatic triglyceride lipase activities were both decreased to $0{\cdot}5\ \mu\text{mol ml}^{-1}\ \text{h}^{-1}$ and $3{\cdot}0\ \mu\text{mol ml}^{-1}\ \text{h}^{-1}$, respectively. She developed renal failure, respiratory infection, diabetes mellitus due to pancreatitis and hepatic failure. Cessation of tamoxifen together with haemodialysis and plasma exchange rapidly decreased both triglyceride and total cholesterol levels, but she died of hepatic failure on 2 July 1984. The autopsy confirmed the clinical findings of metastases mainly in the lungs, a huge fatty liver, chronic pancreatitis and pulmonary congestion, but no metastasis was histologically found in the liver.

Discussion

The side effects of tamoxifen have been widely documented. They included anorexia and nausea, hot flushes,

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thrombocytopenia, leucocytopenia, depression, migraine, hypercalcaemia, rash, periorbital and peripheral oedema, pruritis, thrombosis, tiredness, sweating, vaginal bleeding, metallic taste in mouth and peripheral neuropathy[4,5].

Tamoxifen is anti-oestrogenic but has a weak intrinsic oestrogen activity on protein metabolism. Recently, Rossner and Wallgren[1] reported on the variations in plasma lipoprotein composition produced by tamoxifen therapy. They suggested that those effects of tamoxifen on lipoprotein may be secondary to some oestrogenic properties. Indeed, they also observed a reduction of orosomucoid and hepatoglobin concentrations, similar to those occurring with the administration of oestrogens or during pregnancy. Oestrogenic agents depress post-heparin lipolytic activity and hepatic triglyceride lipase (h-TGL), and increased plasma triglycerides[6,7]. Brun *et al.*[2] reported similar results which suggested an oestrogenic effect of tamoxifen in a patient with severe hypertriglyceridaemia. It is admitted that, in normal subjects, plasma low density lipoprotein originates mainly from hydrolysis of plasma very-low density lipoprotein triglyceride under the action of lipoprotein lipase and h-TGL[8]. In Brun's[2] and our patients, lipoprotein lipase and h-TGL activities were both decreased while on tamoxifen. Their specific inhibition by tamoxifen, however, does not seem to exert a main effect on the clearance of plasma triglycerides[7,8]. Triglyceride turnover demonstrated that hypertriglyceridaemia associated with oestrogen therapy is due to increased triglyceride synthesis without impairment of its removal[9]. Removal of plasma triglyceride is a saturatable process[10]. When some patients with a pre-existing hyperlipoproteinaemia, in which plasma triglyceride levels may be elevated near the point of saturation before oestrogen therapy, are put on tamoxifen therapy, large increases in lipid levels can occur. In our patient, it produced a fatal complication. We suggest that serum triglyceride and cholesterol levels should be measured routinely before such therapy, and as long as the patients are treated with tamoxifen.

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Paper accepted 12 December 1986

Br. J. Surg. 1987, Vol. 74, July,
588–590

Activated oestrogen receptor in human breast cancer: clinical and biochemical correlates

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The oestrogen receptor (ER) contains a DNA-binding site, the activity of which can be determined by its binding to oligo(dT)-cellulose. In premenopausal women with breast cancer, 53 per cent of ER-positive tumours were capable of binding to oligo(dT)-cellulose (activated ER); the corresponding proportion in postmenopausal patients was 70 per cent ($P<0\cdot005$)*. Disease recurrence was significantly increased in patients whose tumours contained non-activated rather than activated ER. The presence of activated ER was associated with a significant increase in the median activity of creatine kinase in premenopausal and postmenopausal patients. In postmenopausal patients the incidence of progesterone receptor was higher in tumours that contained activated ER than in tumours that contained ER not capable of binding to oligo(dT)-cellulose (non-activated). The incidence of activated ER was not related to disease stage or nodal involvement at the time of sampling. The data suggest that ER-positive tumours can be divided, according to the activity of the DNA-binding site, into subgroups with differing biological properties.*

Keywords: Breast cancer, activated oestrogen receptor, disease recurrence

Steroid hormones specifically interact with receptors which are believed to mediate hormone action by their association with DNA elements and activation of selected genes[1]. The oestrogen receptor (ER) contains separate hormone and DNA-binding sites which can be distinguished biochemically[2] and immunologically[3]; the predicted amino acid sequence of these separate domains has recently been reported[4].

Routine ER analysis in human breast cancer provides information about incidence based on the interaction of oestradiol with the hormone-binding domain of the receptor. The incidence of ER is associated with improved survival[5,6] but not disease-free interval[5–7]. In one study, however, a significantly longer disease-free interval was reported in patients whose primary tumour contained nuclear oestrogen receptor together with cytosolic receptor[8]. It is well established that ER can exist with its DNA-binding site in different activation states[2] and that activation of the DNA-binding site is paralleled by an increased capability to bind to nuclei[9]. Hitherto little attention has been given to the DNA-binding capacity of ER and to the possibility that human breast cancer ER may exist with defective DNA-binding properties, as reported in model systems[10]. The activity of the DNA-binding site of human breast cancer ER has therefore been assessed by the binding of cytosolic ER to oligo(dT)-cellulose[11]. The objective of this study was to determine whether evaluation of activated ER could provide additional information on disease recurrence not provided by oestradiol-binding measurements alone.

If differences in the ability of human breast cancer ER to bind to oligo(dT)-cellulose reflect the affinity of ER for nuclei *in vivo*, and hence receptor function, then differences in biochemical products of oestrogen action would also be expected. Therefore the incidence of progesterone receptor (PR) and the activity of creatine kinase, each being oestrogen-sensitive[12,13], has been analysed in relation to the ability of ER to bind to oligo(dT)-cellulose.

Patients and methods

Four hundred and eighty-one primary breast cancers, treated by mastectomy or lumpectomy at Hammersmith Hospital and several referral hospitals, were assayed for ER. The binding of ER to oligo(dT)-cellulose was investigated in 273 of 280 ER-positive samples, 83 from premenopausal and 190 from postmenopausal patients. Accurate clinical data on tumour staging (TNM classification) was available on 262 patients. Of these, 84 ER-positive and 63 ER-negative patients with stage I–III disease and treated at Hammersmith Hospital, were evaluated for recurrence of disease at a minimum period of 12 months following surgery (median 36 months, range 12–64). They had not received chemotherapy or any other therapy postoperatively, except radiotherapy where there was nodal involvement.

Frozen tissue (stored in liquid nitrogen) was pulverized in a microdismembrator (Braun Instruments Ltd, FRG) and the powder resuspended in buffer (10 mM phosphate; 1·5 mM EDTA; 1 mM dithiothreitol (DTT); 30 per cent glycerol, pH 7·4) to a concentration of 1:8 (w/v) and allowed to stand on ice with intermittent vortexing for 15 min. A cytosol preparation was obtained by centrifugation of the homogenate at 200 000*g* for 1 h at 4°C and an aliquot of this was incubated in the presence of ^{3}H-oestradiol (final concentration 5×10^{-9}M) with and without a 200-fold molar excess of diethylstilboestrol (DES) at 4°C for 18–24 h to measure ER. Progesterone receptor was similarly determined using ^{3}H-progesterone (final concentration 10^{-8} M) and cortisol (10^{-6} M) with and without a 100-fold molar excess of unlabelled progesterone (10^{-6} M). Following incubation, aliquots of cytosol (200 μl) were added to an equal volume of 0·5 per cent charcoal and 0·05 per cent dextran T-70 suspension in phosphate buffer and incubated at 4°C for 10 min to remove free radioactivity by adsorption. Following centrifugation (2000*g*, 10 min), the supernatant was assayed for radioactivity. Activation of ER was determined by incubating 200 μl of labelled cytosol with 150 mg of oligo(dT)-cellulose prepared as a mini-column, for 45 min at 4°C. Unbound material was removed with 15 ml of phosphate buffer and bound receptor (activated) eluted with 4 ml of phosphate buffer containing 1·2 M KCl. All radioactivity was measured in Unisolve (Kochlight) using an Intertechnique SL-3000 series counter at a constant efficiency of 43 per cent. A value of 10 fmol/mg cytosol protein was used to discriminate between receptor positive and negative specimens. Creatine kinase (CK) activity was measured spectrophotometrically at 340 nM in a mixture containing imidazole acetate (50 mM) pH 6·7, phosphocreatine (9 mM), glucose (5 nM), ADP (2 mM), magnesium acetate (20 mM), NADP (0·5 mM), diadenosine pentaphosphate (40 μM), DTT (5 mM), hexokinase (1 unit, glucose-6-phosphate dehydrogenase (0·5 units) in a final volume of[14] 3 ml at 25°C.

Receptor incidence data were anlysed by χ^2, the activity of CK by the Mann–Whitney *U* test and recurrence data by the log rank test[15].

Results

The incidence of ER-positive tumours in premenopausal patients was lower than in postmenopausal patients (*Table 1*), consistent with observations reported by others[5], and probably reflects the cyclic influence of gonadal steroids during the menstrual cycle. In those tumours that contained ER the ability to bind to oligo(dT)-cellulose was also affected by menopausal status, the incidence of activated ER being lower in the premenopausal group (*Table 2*). The incidence of ER and of activated ER was not associated with disease stage or nodal involvement (*Table 3*).

The proportion of patients remaining disease-free following surgery was not influenced by ER status (*Figure 1*). However, when ER-positive tumours were subdivided according to ability to bind to oligo(dT)-cellulose there was a significant increase in the proportion of patients that remained disease-free in the group that contained activated ER (*Figure 1*).

The median activity of CK was significantly higher in tumours that contained activated ER when compared with non-activated ER or ER-negative tumours (*Table 4*), in both premenopausal and postmenopausal patients. The incidence of progesterone receptor was significantly increased in tumours that contained activated ER in postmenopausal but not premenopausal patients (*Table 5*).

Discussion

Recent evidence indicates ER to be predominantly associated with nuclear structures *in vivo*[16,17]. Nevertheless, data derived from the measurement of cytosol ER (apparently solubilized during tissue preparation) provides information on hormonal sensitivity and disease prognosis in human breast cancer[18]. Similarly measurement of the DNA-binding capacity of ER in the soluble fraction is associated with the biological properties of experimental rat breast tumours[10].

Table 1 *Incidence of oestrogen receptor (ER) in malignant breast cancer specimens in relation to menopausal status*

	Premenopausal	Postmenopausal
Number of tumours	188	293
Number of ER-positive	85*	195
Percentage ER-positive	45·2	66·6

* Significantly different from postmenopausal: $P<0·0005$, $\chi^2=21·44$

Table 2 *Incidence of activated oestrogen receptor (ER) in the ER-positive specimens described in* Table 1

	Premenopausal	Postmenopausal
Number of ER-positive tumours investigated for activated receptor	83	190
Number of tumours containing activated ER	44*	133
Percentage activated ER	53·0	70·0

* Significantly different from postmenopausal: $P<0·005$, $\chi^2=7·31$

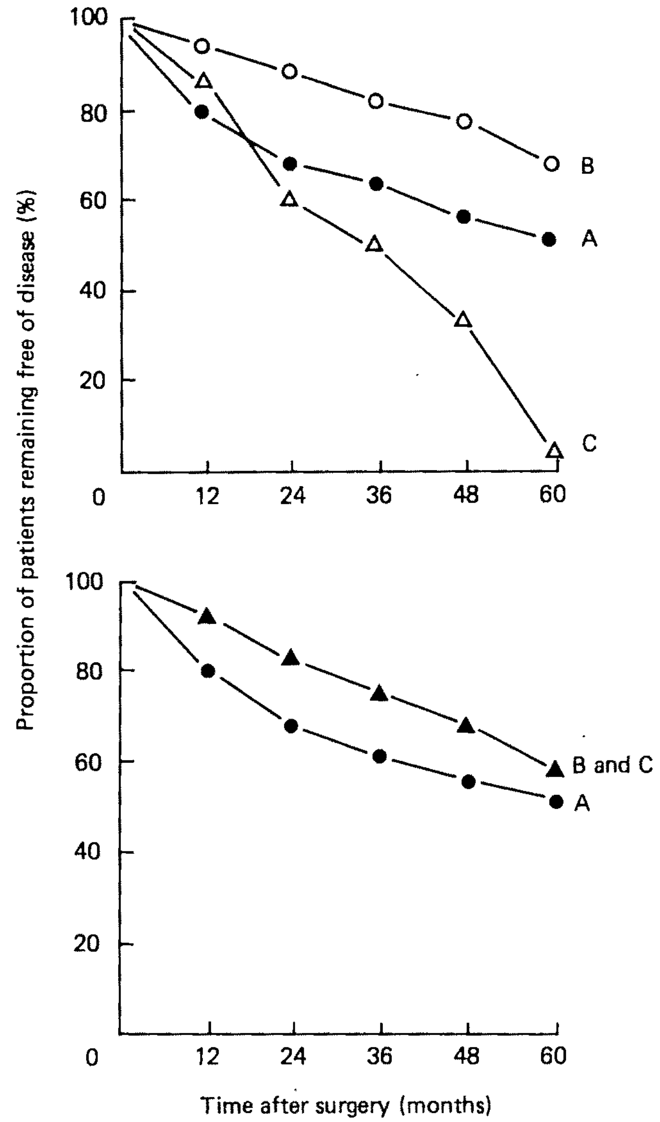

Figure 1 *Disease recurrence and activated oestrogen receptor (ER). The proportion of patients remaining free of disease at each time interval for ER-negative (A), activated (B) and non-activated (C) tumours. The data were derived from the number of patients at risk* (n) *and the number of recurrences (R) in each time interval as indicated below. Statistical analysis was by the log rank method*[15]

	(A) ER negative		(B) ER activated		(C) ER non-activated	
Months	*n*	R	*n*	R	*n*	R
0–12	63	12	63	3	21	3
13–24	49	7	60	4	17	5
25–36	36	3	46	3	12	2
37–48	23	2	33	2	6	2
49–60	12	1	16	2	1	1

ER activated significantly different from ER negative: $\chi^2=5·05$, $P<0·025$

ER activated significantly different from ER non-activated: $\chi^2=13·76$, $P<0·0005$

Table 3 *Incidence of oestrogen receptor (ER) and activated ER in relation to stage of disease and to nodal involvement in malignant breast cancer specimens*

	Disease stage (TNM classification)				Nodal status	
	I	II	III	IV	Negative	Positive
ER	28/41 (68·3%)	93/139 (66·9%)	33/45 (73·3%)	20/37 (54·1%)	90/127 (70·9%)	82/132 (62·1%)
Activated ER	21/28 (75·0%)	67/93 (72·0%)	24/33 (72·7)	14/20 (70·0%)	68/90 (75·6%)	61/82 (74·4%)

Table 4 *Activity of creatine kinase (CK) in relation to activated and non-activated oestrogen receptor (ER) in malignant breast cancer specimens*

	CK activity (milliunits/mg protein)	
	Premenopausal	Postmenopausal
ER negative		
Median	35·7	37·0
Range	7·1–221·5	5·0–498
Number of tumours	31	27
ER-positive non-activated		
Median	30·6	38·9
Range	6·2–202	10·5–443
Number of tumours	17	29
ER-positive activated		
Median	58·0*†	61·0*‡
Range	26·2–195	12–448
Number of tumours	11	40

* Significantly different from ER negative: $P<0{\cdot}04$

† Significantly different from ER-positive non-activated: $P<0{\cdot}04$

‡ Significantly different from ER-positive non-activated: $P<0{\cdot}02$

Statistical analysis by Mann–Whitney *U* test

Table 5 *Incidence of progesterone receptor (PR) in malignant breast cancer specimens from premenopausal and postmenopausal patients in relation to activated and non-activated oestrogen receptor (ER)*

	Incidence of PR	
	Premenopausal	Postmenopausal
ER-positive non-activated	22/39	37/57
ER-positive activated	37/44	103/133*

* Significantly different from ER-positive non-activated: $\chi^2=3{\cdot}23$, $P<0{\cdot}05$

The ability of human breast cancer ER to bind to oligo(dT)-cellulose has both clinical and biochemical correlates. In agreement with some other reports, there was no significant difference in the disease-free interval of patients according to ER status[5–7]. However, our data clearly demonstrate that ER-positive tumours should be considered as subgroups according to their ability to bind to oligo(dT)-cellulose. Tumours that contained activated ER had the most favourable prognosis, which was significantly different from that of non-activated ER and ER-negative groups. There was no significant difference between non-activated ER and ER-negative groups with respect to disease-free interval. The major proportion of ER-positive tumours (63/84; 75 per cent) are therefore in a different risk category from ER-negative tumours. The incidence of activated ER was not related to nodal involvement or stage of disease, suggesting that these prognostic factors[5] do not underlie the effects of activated ER on disease-free interval. (This aspect will be further investigated as more patients become available for clinical assessment.)

The median activity of CK was significantly higher in tumours that contained activated ER. However, there was a considerable overlap of values between the ER-negative group and the two ER-positive subgroups.

Activated ER was not an absolute determinant of progesterone receptor status although in the presence of activated ER the incidence of PR was significantly increased in postmenopausal patients. The steady state levels of CK and PR are, like other proteins, determined by their synthesis and degradation. In order to demonstrate any association between activated ER and CK or PR it may be necessary to investigate their response to hormonal stimulation. Preliminary results indicate that CK is sensitive to short-term tamoxifen treatment (Philipson *et al.*, unpublished).

In conclusion we suggest that the presence of activated ER distinguishes a group of patients with tumours having distinct biological properties and that it is a parameter that should be considered in the management of human breast cancer. It is intriguing to propose that the discordance between reports of a relationship between ER and disease-free interval, previously attributed to an influence of adjuvant endocrine treatment in certain studies[7], may reflect an effect of such treatments on receptor activation.

Acknowledgement

We wish to thank Hammersmith Special Health Authority, Man of the People and the Sir Halley-Stewart Trust for their financial support.

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Paper accepted 6 March 1987

Br. J. Surg. 1987, Vol. 74, July,
591–593

Carcinoma of the breast in women aged 35 or less

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Breast cancer in young women is an unusual problem which has acquired a poor prognostic reputation in the eyes of many clinicians. We have reviewed all 59 patients with malignant disease of the breast aged 35 years or less managed in the Breast Unit at Charing Cross Hospital between 1974 and 1984. After exclusion of 5 patients (2 with lymphomas, 1 with fibrosarcoma, and 2 with inadequate available data), 54 patients were available for analysis. More than 3 months delay from first symptoms to presentation was seen in 45 per cent and 36 per cent were considered 'late' at initial clinical staging (T_{3-4}, N_{2-3} *or* M_1)*. Nevertheless, a 5-year survival of 66 per cent was seen among the 29 patients with sufficient length of follow-up. Distribution among the main histological types was very similar to that found in a consecutive series of 264 breast cancers of all age groups in our unit. We conclude that breast carcinomas in young patients do not significantly differ in type or behaviour from other age groups and that with treatment similar to other premenopausal patients, a prognosis comparable to older patients can be expected.*

Keywords: Breast cancer, young women, malignant

Breast cancer in women aged 35 years or less is unusual but not rare. It may present particularly difficult management problems when occurring during pregnancy, lactation, or in patients with a young family. It is commonly believed that the disease in this age group differs in behaviour, type and prognosis from that seen in older patients[1,2]. If so, treatment policies may need to be altered to allow for such variations.

In 1880, Gross stated 'the rate of growth (of breast cancer) is not, contrary to the generally received opinion, influenced by the early age of the patient'[3]. Since then, many studies have suggested that prognosis in the young is similar to that in older patients[4–6], while others disagree[1,2]. Brightmore *et al.* reviewed 101 cases of breast carcinoma in women under 35 years and found an increased proportion of tumours of higher grade malignancy than expected[7]. Although survival compared grade for grade and stage for stage was similar to older patients, more high grade tumours biased survival against the younger age group. In contrast, Treves and Holleb reviewing 549 young cases of breast cancer found survival to be no different from other age groups[8].

Particular histological tumour types have been reported more frequently in certain age groups; medullary carcinomas appear to be more common in the young and infiltrating lobular carcinomas more frequent in the elderly[9,10]. Whether these types relate to the biological behaviour of the tumour and therefore our approach to treatment is less clear, although variations in prognosis are associated with certain histological types[11].

Since the literature over the years has been either confusing or contradictory we have reviewed our experience of breast carcinomas presenting in women aged 35 years or less to one specialist unit. We aimed to investigate whether breast carcinoma in the young behaved similarly to that in older patients and therefore whether it should be managed in a similar manner.

Patients and methods

All 59 patients with cancer of the breast aged 35 years or less at diagnosis referred to the Breast Unit at Charing Cross Hospital between 1974 and 1984 were reviewed. This was about 4 per cent of all new breast cancer patients seen over this period. Some have been included who were diagnosed elsewhere but referred to our unit for further management during the review period. In five of these patients, the initial diagnosis was made before 1974 so the maximum follow-up was 18 years. Information was gathered from patients' hospital case notes with review of histological material when available. Five patients were excluded from the study; three had tumours other than adenocarcinomas (two lymphomas and one fibrosarcoma) and in two cases inadequate data or follow-up was available. This left 54 patients for analysis.

Details of presenting symptoms and their timing, family history, age at menarche and oral contraceptive use were sought. Stage at presentation was analysed in all cases where the UICC system (TNM)[12] had been applied ($n=50$). Histological types were reviewed and the proportions of each type compared with those found in a consecutive series of 264 breast cancers of all ages seen at Charing Cross Hospital. Hormone receptor assays were not performed during the earlier years of the study so results were available on too few patients for worthwhile analysis. Methods of treatment were reviewed and follow-up and survival was assessed overall as well as in stages.

Results

Ages ranged from 21 to 35 years with a mean of 31 years. There was a strong bias towards the upper age limit with 42 (78 per cent) patients presenting between 30 and 35 years, and only 12 (22 per cent) under 30 years (*Figure 1*).

Presenting symptoms

The time from the patient's first breast symptom until presentation was only accurately documented in 33 cases and in 15 (45 per cent) of these it was more than 3 months before hospital attendance with 4 (12 per cent) delaying more than a year. The patient herself noticed a lump in all but two cases though sometimes combined with other symptoms. In these two cases, one noted pain and the other skin changes. None of this series were diagnosed at routine medical checks.

Family and personal history

A positive family history of breast cancer is reported more frequently in young breast cancer patients[13], but was only found in three of our cases and in one of these the relative was male. One patient had a grandmother, mother and sister all developing carcinoma of the breast at an early age, the sister being diagnosed at the age of 25 years. Although long-term use

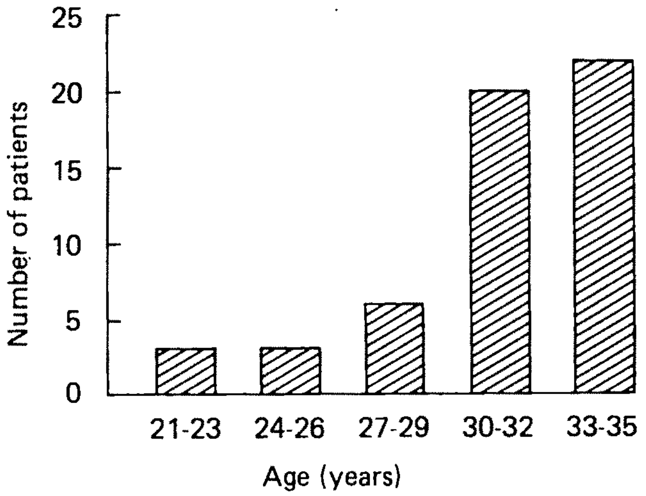

Figure 1 *Age distribution at presentation with a mean of 31 years. Only 12 patients (22 per cent) were under 30 years at presentation*

Table 1 *Main histological types of the under-35 age group compared with those in a consecutive series of 264 invasive breast carcinomas of all age groups seen at Charing Cross Hospital*

Histological type	<35 years ($n=38$)	All ages ($n=264$)
Invasive ductal	30 (79%)	203 (77%)
Invasive lobular	5 (13%)	37 (14%)
Medullary	1 (3%)	15 (6%)
'Unusual' Tubular Mucoid Papillary Squamous	2 (5%)	9 (3%)

Intraduct carcinomas without invasion, of which five were seen in the young group, are not included

of oral contraceptives before the age of 25 is said to increase the risk of subsequent breast carcinoma[14], only three in our series had done so for more than 5 years, although 45 per cent had used oral contraceptives at some time. Nearly two-thirds of the patients (61 per cent) had at least one child and six (11 per cent) presented during pregnancy or lactation. Of these six, all have either died or have recurrent disease though two survived at least 10 years.

Stage at presentation

Based on the clinical TNM stage at presentation patients were divided into 'early' or 'late' groups. Of the 54 patients studied, 4 who were initially treated elsewhere were staged by other methods, leaving 50 to analyse. 'Early' was defined as T_{0-2} N_{0-1} M_0 and the remainder as 'late' presentations. Only 32 (64 per cent) came within the early group, and 18 (36 per cent) presented late, of whom 4 (8 per cent) had distant metastases.

Histology

Tumours were grouped into major histological types by review of histological material or from sufficiently detailed original reports. Eleven patients could not be accurately grouped and original material was unavailable for review. Of 43 cases, 5 were intraduct and 38 invasive, of which 30 were ductal and 5 lobular invasive tumours with only one each of medullary, mucoid and papillary varieties. Comparison of this series with a review of 264 consecutive breast carcinomas of all ages seen in the same unit showed a very similar distribution (*Table 1*).

Treatment

Our general policy was to advise mastectomy in early cases only, and more advanced disease was treated systemically, sometimes combined with local radiotherapy. In this series mastectomy was performed in 39 patients, being simple total in 25 and radical in 14. The remaining 15 patients underwent eithe biopsy or segmental excision combined with radiotherapy or systemic therapy. As part of their primary treatment 15 patients underwent ovarian ablation combined with local treatment o radiotherapy in 7 cases and biopsy alone in 4. Four mastectomy patients also had ovarian ablation primarily, usually fo unfavourable histological indications. Other forms of hormona manipulation or cytotoxic chemotherapy were generally reserved for recurrent disease or failure to respond to initia therapy.

Follow-up

Follow-up ranged from 6 months to 18 years with a mean of 4· years. Thirty-eight (70 per cent) patients were alive at las follow-up but 13 (24 per cent) had known recurrent disease. O the initial series 16 (30 per cent) have died a mean of 4 years afte diagnosis. Analysis of 5-year survival was possible in 29 patients and of these 19 (66 per cent) were alive at 5 years. Dividing thes 29 patients into 'early' or 'late' presentations, 18 of the 22 'early cases (82 per cent) were alive at 5 years (*Figure 2*). Confirmin the prognostic importance of histological nodal assessment only 2 of the 18 clinically 'early' 5-year survivors ha histological evidence of nodal involvement but 3 out of 4 wh died had nodal spread.

Discussion

Individual surgeons or oncologists will only manage breas cancer in the under-35 age group infrequently. McWhirte calculated that even including breast cancer patients up to th age of 40 years, each general practitioner is only likely to see on such case every 15 years of his working life[15]. Misconception easily arise about any uncommon condition, particularly whe the literature appears contradictory. Therefore careful review o one's own experience and that of others is valuable in plannin the future management of young breast cancer patients.

Greater media emphasis on health matters in general and th early detection of breast cancer in particular, wit encouragement for women to carry out regular self examination, might have increased early presentation especially among younger patients. The delays from first symptoms in ou series were disappointingly long with only 55 per cen presenting within 3 months, whereas 56 per cent in Treves an Holleb's report from 1958 and 68 per cent from that o Brightmore *et al.* in 1970 presented in the same time. Certainly

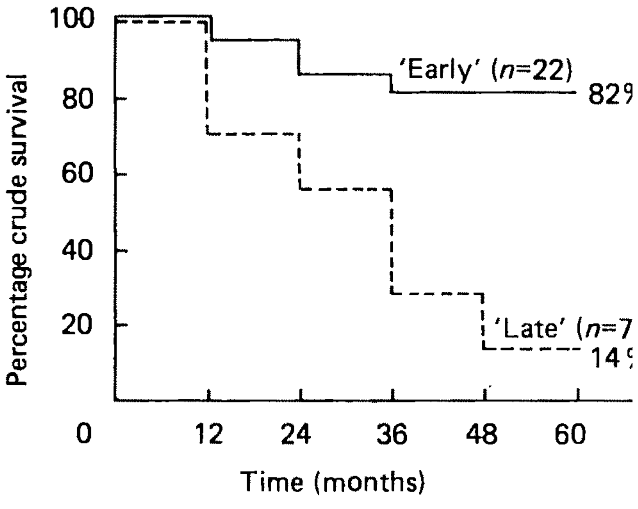

Figure 2 *Five-year survival for the 29 patients with sufficient length o follow-up. Of these, 22 were classified as 'early' on clinical assessment an showed an 82 per cent 5-year survival*

this does not suggest any improvement in patient education unless there are delays at primary referral. Although disputed by some, it is generally agreed that delay from first symptoms to presentation carries a poorer prognosis[16,17].

Treatment policies evolved to some extent during the review period and a few patients received primary treatment elsewhere, so significant conclusions about individual methods could not be drawn. The majority of 'early' cases were treated by mastectomy with or without radiotherapy. Hormonal manipulation was only added at the initial stage if histological findings and nodal spread suggested a poorer prognosis. Ovarian ablation was usually recommended in 'late' cases and radiotherapy for local disease was reserved for those failing to respond. Chemotherapy was generally used in patients not responding to hormonal manipulation or with recurrence after initial response. This formed the basis of therapy for all premenopausal patients including those in the under-35 age group.

Turning to the question of prognosis, although follow-up is relatively short in the more recent cases, there were 29 patients with a full 5-year follow-up. The overall 5-year survival of 65·5 per cent among these patients compares favourably with various large series of older breast cancer patients in which 5-year survival is reported to vary from 56·4 per cent to 59·6 per cent[18,5,4] and certainly suggests that the prognosis in younger patients is no worse than other age groups.

Histological types of breast carcinoma may be relevant to biological behaviour so proportions of each main type in the young patients were compared with those found in a series of all ages at Charing Cross Hospital and a series from McDivitt *et al.*[11]. In all three, the percentages of the main types are very similar but small numbers of the unusual varieties preclude firm conclusions for these. Medullary carcinomas are reported to be more common in younger patients[5]; however, most patients with medullary carcinomas (both typical and atypical) in our study of all age groups were between 35 and 50 years and only one was under 35.

The problem of pregnancy and breast cancer always presents great difficulty and the prognosis is considered poor[19,20]. Our series included six patients with breast cancer diagnosed during pregnancy or lactation and although none remain disease-free, two survived more than 10 years. The question of subsequent pregnancy in breast cancer patients is often discussed. Experience from our series is limited but Peters suggested subsequent pregnancy not only fails to worsen prognosis but actually improves it[21].

In conclusion we were most disappointed by the delays in presentation which implied that in young patients at least no gains have been made towards earlier diagnosis as a means of improving survival. All parameters we examined suggested that breast cancer occurring before the age of 35 years was similar in type, behaviour and prognosis to that found in other age groups. We would advise that treatment for patients unfortunate enough to develop carcinoma of the breast at this young age should be similar to other premenopausal women and a similar prognosis expected. Particular attention should be paid to the need for social and psychological support especially when a young family is involved.

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Paper accepted 6 March 1987

Br. J. Surg. 1987, Vol. 74, July, 594–596

Early surgical history of phaeochromocytoma

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Keywords: Surgery, history, phaeochromocytoma

A century ago, in 1886, Dr Felix Fränkel of Freiburg im Breisgau published an account of Fräulein Minna Roll, aged 18, who for a year had suffered intermittent attacks of palpitation, anxiety, vertigo, headache, vomiting and constipation[1]. Her pulse was rapid and strong and the artery was tense but, since sphygmomanometers had not yet come into use, her blood pressure was not measured. She was pale and had a goitre. Later she developed retinopathy and her vision deteriorated. She became febrile, dyspnoeic on occasions, developed pain in the chest and broke out in cold sweats. She was admitted to hospital where, despite medication, which included champagne and injections of ether, she died after 9 days, apparently from circulatory failure.

Autopsy revealed bilateral adrenal tumours, one the size of a fist, the other smaller. Histologically they were very vascular, consisted largely of spindle cells and were regarded as angiosarcomas of the adrenal medulla. They were, however, stained with Müller's fluid, which contains potassium dichromate, and showed 'yellow to dark brown areas'. This must be interpreted as a positive chromaffin reaction and it is hard to escape the conclusion that the tumours were phaeochromocytomas (P. Lewis, 1986, personal communication). The kidneys showed recent parenchymatous inflammation, the arteries throughout the body were thickened and the heart was hypertrophied. The nature of the goitre was not described. The only clinical manifestation of adrenal pathology recognized at that time was Addison's disease and, since there were no signs of this, Fränkel attributed the clinical features mainly to nephritis and regarded the adrenal tumours as symptomless ('latent').

Similar adrenal tumours, recognized as medullary in origin but given various names, were described by pathologists within the next few years[2,3] and in 1896 Dr Paul Manasse of Strassburg, Germany (now Strasbourg, France), described a positive chromaffin reaction in several[4]. Identical tumours were soon found in extra-adrenal chromaffin tissue and, in 1908, Drs Alezais and Peyron in Marseilles named these 'paragangliomas'[5]. In 1912 Dr Ludwig Pick of Berlin proposed the name 'phäochromocytom' ('phaeochromocytoma' in English and 'pheochromocytoma' in American) for tumours in the adrenals and at extra-adrenal sites[6]. However, the names were used interchangeably for many years until all eventually came to be called phaeochromocytomas[7].

The syndrome of paroxysmal hypertensive crises observed during life, associated with phaeochromocytomas found at autopsy, had been observed several times since Fränkel's report[8,9], but little attention was paid to it until Dr Marcel Labbé and his colleagues reported a case in Paris in 1922[10]. By this time much was known of the adrenal medulla and adrenaline so that, unlike Fränkel, they attributed the symptoms to the tumour.

Despite this the first few phaeochromocytomas to be treated surgically were not diagnosed before operation. In 1923 Professor Villard of Lyon removed a 'malignant suprarenal paraganglioma' from a patient, who died in shock, which he regarded as disproportionate to the severity of the operation[11].

The first successful removal of a phaeochromocytoma was long attributed to Dr Charles Mayo (*Figure 1*) in 1926 and is recorded in two papers[12,13]. The patient, Mother Joachim, a nun from Ontario, had suffered paroxysms for 18 months, and

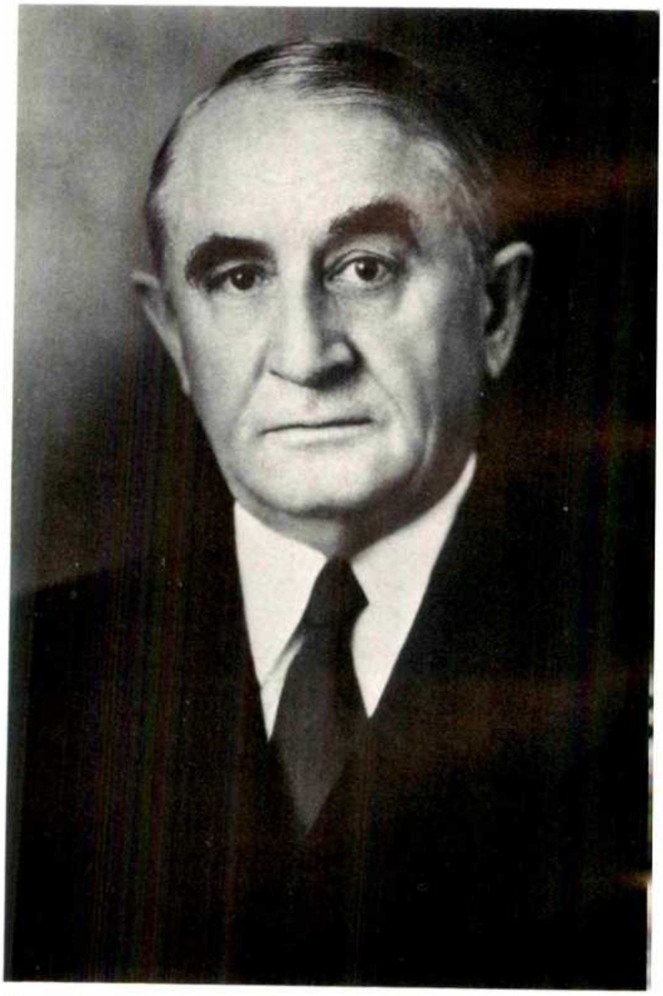

Figure 1 *Dr Charles Horace Mayo (1865–1939), reproduced by courtesy of the Mayo Clinic*

Based on a paper presented to the International Surgical Group, Birmingham, UK on 4 September 1986

Figure 2 *Professor César Roux (1857–1934), reproduced by courtesy of Professor Frédéric Saegesser*

the referring physician wrote 'I feel much as Festus felt in sending Paul to Rome, not having any definite accusation against him'. The blood pressure rose on occasions to 320/160 mmHg, but there were no abnormal signs between attacks. The Mayo physicians did not suspect a phaeochromocytoma, although Labbé's paper had been published 4 years previously. Rather, they thought that the symptoms were mediated through the sympathetic nerves and that cervical sympathectomy by Dr Alfred Adson might help. Mayo felt that 'toxins were intermittently discharged' and, since *lumbar* pain was a feature of the attacks, by good fortune suggested that an approach through the *splanchnic* nerves by laparotomy might prove more beneficial. He operated on 9 October 1926 and found a tumour, the size of a lemon, behind the tail of the pancreas, apparently separate from the adrenal. He removed it uneventfully and the pathologists gave it various names, including 'retroperitoneal malignant blastoma'[12] and an 'encapsulated fibrous cellular retroperitoneal malignant neoplasm[13]. Recent examination by Dr Aidan Carney shows it to be a typical phaeochromocytoma with adrenocortical tissue at the edge of the section (J. A. Carney, 1986, personal communication). There was no mention of the blood pressure during or immediately after operation, but recovery was rapid, all the symptoms ceased and the systolic pressure remained at 120–130 mmHg thereafter. The patient remained well for 18 years, eventually dying from a coronary thrombosis.

The first general intimation that a phaeochromocytoma had been removed successfully before this came in a paper by Dr André Barbeau and his colleagues from Montreal in 1958[14]. They wrote (in French) that 'Roux in France (*sic*) and Mayo in the United States opened the way to surgical treatment', and gave as their reference a thesis by Roux in Lausanne in 1926. This reference was mentioned by others without verification[8,15]. The University Library at Lausanne (in Switzerland not France) has no record of this thesis (V. Bohanès, 1984, personal communication), but does possess one presented for an MD, by Dr Roland von der Mühll, a physician working in the Department of Pathology, published in 1928[16]. The thesis is only 32 pages in length, 12 of them reporting Roux's patient.

César Roux (*Figure 2*) had been assistant to Professor Theodor Kocher in Berne and was Professor of Surgery at Lausanne from 1890 to 1926. Dr Harvey Cushing had visited him in 1900 and described him as a rough diamond, doing excellent work, and wrote that he enucleated goitres, without anaesthetic or morphia, in 8–12 min[17]. He is best known generally for the Roux-en-Y anastomosis.

In the year that he retired Madame S. came to his clinic, having suffered attacks of vertigo and nausea for 2 years. These may have been hypertensive crises, but blood pressure is not mentioned anywhere in the thesis. Then she noticed a lump, the size of an orange, under her right costal margin and X-rays suggested a primary hepatic tumour. On 25 February 1926, 7 months before Mayo's operation, Roux did a laparotomy and removed the tumour, which was attached to the right adrenal. The patient recovered uneventfully and remained well for at least 18 months. The published histopathological sections show a typical phaeochromocytoma.

In 1926, then, on 25 February César Roux did the first known successful operation for removal of a phaeochromocytoma, in Lausanne, and on 9 October Charles Mayo did the second, in Rochester, Minnesota, USA. In 1927, on 13 November, Mayo's paper was published, and on 9 December Mühll's thesis was approved. In 1928 the thesis was published. Neither Roux's nor Mayo's tumour was diagnosed beforehand. Both surgeons were fortunate in the lack of cardiovascular complications during and after operation. César Roux's part in this, together with a general account of his life and work, was published in 1984 by Professor Frederick Saegesser of Lausanne[18].

In 1926, the year of these operations, Drs H Vaquez and E Donzelot in Paris diagnosed a phaeochromocytoma in life, but were unable to locate it[19]. Dr Charles Laubry treated the adrenal areas with X-rays with apparent benefit for 6 months, after which the symptoms recurred[20]. Operation was urged, but the patient died before it could be undertaken and the presence of a tumour was confirmed post mortem. Next, in 1928, Dr Maurice Pincoffs of Baltimore also diagnosed, but failed to locate, a phaeochromocytoma in life[21]. Dr Arthur Shipley operated twice, first doing an exploratory laparotomy and then, 2 weeks later, using a right-sided incision to remove it[22]. The patient suffered severe shock, but recovered. A year later Dr Miles Porter and his son, from Fort Wayne, Indiana, reported a similar case[23]. Accounts of operations continued to appear until, by 1940, about 20 successful ones had been reported, but also at least 10 deaths from operative shock[24,25]. These included three from the Mayo Clinic[26] and two by Dr Alexander Brunschwig from Chicago[27,28].

The diagnosis of phaeochromocytoma was very difficult and many tests, including the use of pharmacological agents, were introduced. The best at this time were histamine to provoke hypertension[29] and phentolamine to reduce it[30]. Catecholamines were measured in the blood and urine in a few centres. The localization of suspected tumours was also difficult. Pyelography was used frequently and proved positive in over half the patients. Perirenal insufflation with gas, used less often, was slightly more helpful, but prone to complications[31].

By 1951, however, 125 operations had been reported, with 33 deaths, and *hyper*tensive storms during operation, in addition to *hypo*tensive crises after, were described in many[31]. Dr John Graham of Boston had operated on nine of the patients – the largest personal series at that time – and all had recovered. He employed intratracheal gas–oxygen–ether anaesthesia and made a point of occluding the venous return of a tumour as soon as possible. For *hyper*tension during operation he crushed the splanchnic nerve and injected amyl nitrite and, in his last two cases, a new short-acting adrenergic blocker. For *hypo*tension he infused blood and adrenaline. Noradrenaline had just become available, but he had not had the opportunity to use it.

Five years later, in 1956, Dr James Priestley and his colleagues at the Mayo Clinic reported a remarkable series of 51 patients[32]. All had been diagnosed in life, mostly with the help of the histamine and phentolamine tests and measurement of catecholamines in the blood. They used plain X-rays and intravenous urograms only to locate the tumours, because they did not consider it necessary to know the site of a phaeochromocytoma before operation. Instead, they used a long transverse epigastric incision which allowed exploration of the whole abdomen and excision of tumours from both sides. Priestley removed 61 tumours from these 51 patients without an operative death. These superb results were the outcome of close cooperation between physicians, surgeons, anaesthetists, pharmacologists and nurses, and the use of two new specific therapeutic aids, namely phentolamine for hypertension and noradrenaline for hypotension. By 1960 the series included 69 patients, one of whom had died without the tumour being found at operation[33].

Several other smaller series were reported at about the same time, with similar excellent results[15,34,35]. However, it was not until new adrenergic blocking agents and adequate measures to expand the blood volume came into use in the 1960s that the alarming hazards of operations for phaeochromocytomas were finally overcome and that surgeons in general were able to match these achievements[36,37].

Acknowledgements

I am grateful to: The Ahmanson Foundation, The Henry J. Kaiser Family Foundation and The Yvonne Gregory Fund, which supported the work; Miss E. A. Davis, Assistant Librarian at the RPMS, who obtained most of the references; Dr P. Lewis of the RPMS for his help with the interpretation of Fränkel's pathological report; Dr J. A. Carney of The Mayo Clinic, who re-examined the sections of the tumour removed by Mayo; Mr O. Khan, who translated the German papers, Professor F. Saegesser and Mrs V. Bohanès, Head Librarian of the Library of the Medical Faculty at the University of Lausanne, who searched the records and provided me with a copy of Mühll's thesis; and Mrs K. Wilder for secretarial assistance.

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Paper accepted 31 January 1987

Surgical workshop

Br. J. Surg. 1987, Vol. 74, July, 597

Inferior vena cava involvement by a phaeochromocytoma

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Inferior vena cava (IVC) involvement by adrenal phaeochromocytoma is rare. At present only seven cases have been recorded in the world literature and two of these were recurrent tumours[1-6]. For any tumour with caval involvement, the problem is one of surgical access. Dissection of the IVC also carries a high risk of embolization of the tumour. This report describes a novel approach to right adrenal phaeochromocytomas with IVC extension above the diaphragm.

Case report

A 27-year-old hypertensive man was found to have a phaeochromocytoma. A meta-iodobenzyl guanidine (MIBG) scan showed a marked increased uptake in the area of the right adrenal gland and an ultrasound scan revealed an adrenal mass on the right associated with tumour extension up the IVC (*Figure 1*) to within 2 cm of the right atrial orifice. Computerized axial tomography (CT scan) (*Figure 2*) and venography confirmed this finding. Subsequent echocardiographic examination confirmed no tumour extension into the right atrium.

At operation a median sternotomy was performed and two slings were put around the IVC, one intrapericardially, and the other just outside the pericardium but above the tumour. Further exposure was obtained by extending the incision along the right subcostal margin. The right triangular and coronary hepatic ligaments were incised to allow rotation of the liver to the left. With the suprarenal portion of the IVC exposed the layer of fibrous tissue extending from the liver to the posterior abdominal wall was excised. The IVC was clamped above and below the tumour extension. A venotomy was performed extending from the involved right adrenal vein up the IVC. The tumour and its extension were mobilized *en bloc* and removed.

The tumour specimen weighed 235 g and histology suggested a benign phaeochromocytoma. No capsular invasion was present.

Discussion

Phaeochromocytomas may be localized by a combination of MIBG scanning and CT scanning. However, in the unusual situation of caval extension these methods failed to define the degree of IVC invasion. The advantage of real-time ultrasound is that the mobility within the caval lumen may be demonstrated and hence the risk of possible tumour embolism[5,6]. Venography was necessary in our patient to exclude vessel wall invasion and to define precisely the relation of the caval tumour to the diaphragm and the heart.

The first successful extraction of IVC tumour was achieved in 1934[7] via a thoraco-abdominal incision, a surgical approach in use to this day. However, the main disadvantage is poor control of the IVC with a real risk of embolism. Furthermore, access may be limited by the liver, particularly when the tumour extends above the diaphragm. The fact that the tumour in our patient was not invading the wall of the cava suggested that it could be removed providing control of the IVC was adequate, with the option to transfer to cardiopulmonary bypass if the patient did not tolerate IVC clamping. Partial sternotomy in combination with a bilateral subcostal incision has been described for access to upper abdominal tumours. However, the sternocostal approach with early control of the IVC and lateral rotation of the liver represents a novel operative approach to caval tumours extending above the diaphragm.

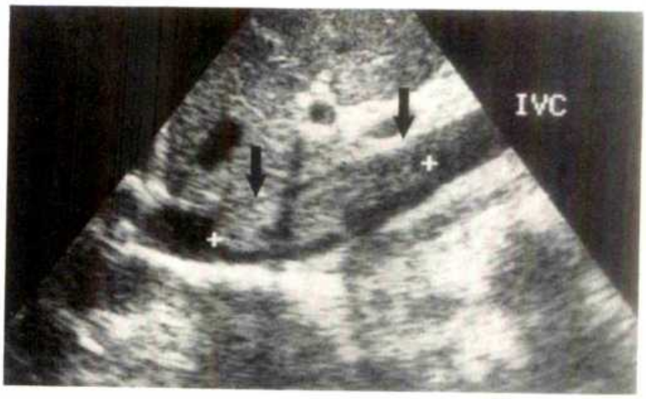

Figure 1 *Longitudinal ultrasound scan reveals tumour extension within the IVC (arrows)*

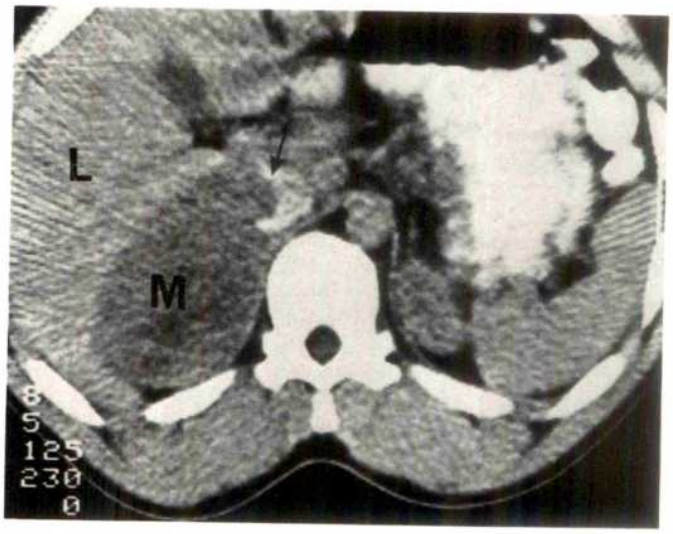

Figure 2 *A CT scan of the upper abdomen shows a massive right-sided adrenal mass (M) with extension into the IVC (arrows)*

Acknowledgements

The authors gratefully acknowledge the assistance of the Department of Diagnostic Radiology.

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Paper accepted 6 January 1987

Case report

Br. J. Surg. 1987, Vol. 74, July, 598–599

Adrenal cortical carcinoma with invasion into the inferior vena cava

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Adrenal cortical carcinoma is a rare, but highly malignant tumour with a short life expectancy, the 5 year survival varying from 16 to 30 per cent[1,2]. It generally presents late in its course with flank pain and a palpable mass[3].

Pre-operative localization of an adrenal tumour and its extension is important from both therapeutic and prognostic standpoints. Most adrenal cortical carcinomas cannot be radically excised because of local invasion, lymph node metastases or distant metastases, most commonly to the lungs and liver[4,5].

We report a case of an adrenal cortical carcinoma with pre-operative ultrasonic demonstration of a tumour thrombus in the inferior vena cava, propagated via the adrenal vein.

Case report

A 72-year-old woman was admitted to the surgical department complaining of right upper quadrant pain, loss of weight and slight swelling of both legs. On clinical examination a right subcostal mass was palpated. The patient was normotensive and, except for a slight elevation of DHEAS (dihydroepiandrosterone sulphate) in plasma, the hormonal and general blood status were normal.

An abdominal ultrasound scan demonstrated a 5 × 2 cm thrombus in the inferior vena cava up to the level of the diaphragm. In addition a 6 × 5 cm solid mass was found just above the upper pole of the right kidney.

The tumour was clearly outlined by computed tomography, and hepatic metastases were not demonstrated. The retrohepatic portion of the inferior vena cava was not visualized, indicating caval involvement. The presence of the thrombus was confirmed by cavography (*Figure 1*).

The tumour and caval thrombus were removed by a combined thoraco-abdominal approach. The caval thrombus was seen propagating into the inferior vena cava from the adrenal vein.

The histological examination revealed an adrenal cortical carcinoma. A repeat ultrasound examination 1 week postoperatively demonstrated a small thrombus (2 × 1 cm) in the inferior vena cava just below the diaphragm.

The patient died 3 months later from extensive thrombosis of the inferior vena cava. At autopsy pulmonary metastases were demonstrated.

Discussion

Computed tomography and ultrasonography represent first line diagnostic methods for evaluating suprarenal masses. Ultrasonic evaluation of the adrenals has been advocated as an accurate, simple and rapid diagnostic procedure[6]. Fine needle aspiration biopsy is widely used in abdominal pathology, and confirmation of an adrenal mass by ultrasound guided biopsy has been reported very helpful and safe[7].

To our knowledge only seven cases have previously been reported with a pre-operative demonstration of caval invasion in adrenal cortical carcinomas (*Table 1*).

Park *et al.*[12] evaluated inferior vena caval obstruction caused by hepatomas, hypernephromas and adrenal cortical carcinomas performing both cavography and ultrasonography. They concluded that ultrasonography is more advantageous in delineation of the cephalad extent of the thrombus, dynamic evaluation of the inferior vena cava below the obstruction and simultaneous evaluation of adjacent organs.

The exact incidence of caval invasion in adrenal cortical carcinomas at the time of diagnosis is not known. Nader[2] found that, of 60 patients with distant metastases from adrenal cortical carcinomas, 6 had caval invasion. In renal cell carcinomas the incidence of caval invasion is approximately 9 per cent[14].

While there is general agreement that caval invasion is an expression of the malignancy of a tumour, some controversy exists as to its prognostic significance. Skinner[15] found a 5 year survival of 65 per cent in patients with renal cell carcinomas confined to the kidney, and a 55 per cent 5 year survival in patients with caval invasion in the absence of distant metastases. Thus, caval invasion, by itself, does not necessarily predict a failure of surgical treatment.

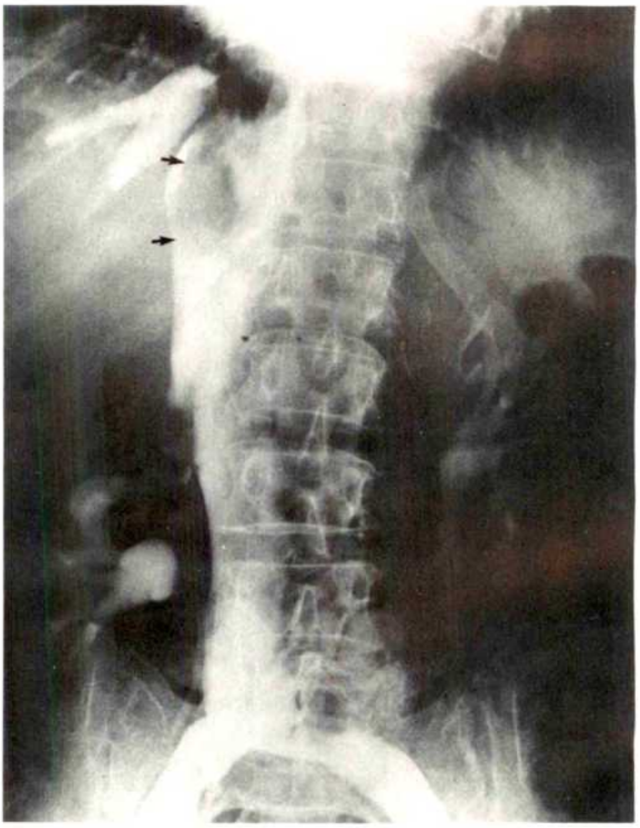

Figure 1 *Inferior vena cavogram (anteroposterior view) demonstrates the tumour thrombus in the inferior vena cava up to the level of the diaphragm (arrows)*

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Table 1 *Literature review. Adrenal cortical carcinoma and caval invasion*

No.	Author	Age	Sex	Tumour	Caval involvement	Cavography	US	CT	Treatment	Outcome
1	Cahill[8]	67	F	Right AC	Retrohepatic	Yes	n.p.	n.p.	Nephrectomy, adrenalectomy, thrombectomy	Alive 5 months without disease
2	Javadpour[9]	22	F	Right AC	Retrohepatic+RA	Yes	n.p.	n.r.	Removal of adrenal tumour+ thrombectomy	Alive 12 months without disease
3	Geelhoed[10]	n.r.	n.r.	Left AC	Retrohepatic	Yes	n.p.	Yes	Adrenalectomy+ thrombectomy	Alive 22 months, lung metastases
4	Geelhoed[10]	n.r.	n.r.	Left AC	Retrohepatic	Yes	n.p.	Yes	Adrenalectomy+ thrombectomy	Alive 22 months without disease
5	Martorana[11]	45	F	Left AC	Retrohepatic	Yes	n.p.	Yes	Removal of tumour, left kidney, spleen, pancreatic tail+ thrombectomy	Alive 5 months without disease
6	Park[12]	n.r.	n.r.	Right AC	n.r.	Yes	n.p.	Yes	n.r.	n.r.
7	Schramek[13]	52	F	Right AC	Retrohepatic+RA	Yes	Yes	Yes	Adrenalectomy+ incomplete thrombectomy*	Died of disease after 5 months. General tumour spread
8	Present case	72	F	Right AC	Retrohepatic	Yes	Yes	Yes	Adrenalectomy+ incomplete thrombectomy	Died of disease after 3 months. Lung metastases. Extensive thrombosis of the inferior vena cava

US, ultrasonography; CT, computed tomography; AC, adrenal cortical carcinoma; RA, right atrium; n.p., not performed; n.r., not reported; * liver metastases at the time of diagnosis

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Paper accepted 20 February 1987

Br. J. Surg. 1987, Vol. 74, July,
600–602

Injection sclerotherapy in adult patients with extrahepatic portal venous obstruction

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Thirty-nine adult and teenage patients with extrahepatic portal venous obstruction (EHPVO) were treated with injection sclerotherapy. There were 22 males and 17 females with a mean age of 27 years (range 12–69). Oesophageal varices were eradicated in 33 patients after seven injections (range 1–17) over a mean of 14·5 months (range 1–48). Fewer injections were needed to eradicate varices in older patients. Variceal bleeding occurred on 13 occasions in 9 patients before eradication of varices and on 4 occasions in 4 of the 33 patients in whom varices had been eradicated, with a mean follow-up of 44 months (range 3–105). There were no deaths during the study period. Complications, mostly of a minor nature, occurred in 25 patients and included injection site leak in 5, stenosis in 7 and mucosal ulceration in 23. We conclude that injection sclerotherapy is the treatment of choice in patients with EHPVO.

Keywords: Injection sclerotherapy, extrahepatic portal venous obstruction

Extrahepatic portal venous obstruction (EHPVO) is the most common cause of portal hypertension in children[1–4]. However, many patients with EHPVO may present for the first time with major variceal bleeding as adults[5,6]. Most previous reports have been limited to children, but have included other intrahepatic causes of portal hypertension and have emphasized the various surgical procedures used in these patients[7–9]. The results of surgery in patients with EHPVO have been far from satisfactory. Recurrent variceal bleeding is common and subsequent surgical procedures have been associated with significant morbidity and mortality[5,6,10].

The natural history of patients with EHPVO has not been well documented. It has been suggested that patients either stop bleeding or bleed less severely and less frequently as they get older[5,7,11]. This trend has made many people adopt a more conservative policy in patients with EHPVO.

We therefore reviewed our experience with injection sclerotherapy in a group of adult and teenage patients with EHPVO.

Patients and methods

Between August 1975 and August 1984, 39 patients with portal hypertension due to extrahepatic portal venous obstruction were admitted to the adult wards of Groote Schuur Hospital, Cape Town. All patients had either suffered previous variceal haemorrhage or were referred specifically with this problem.

There were 22 males and 17 females, with an age range of 12–69 years (mean 27 years). Two patients were under 15 years and ten were over 30 years. Thirty-three patients were grade A and six grade B using a modified Childs' classification system[12].

All patients had routine clinical, biochemical and haematological assessment. The size of the oesophageal varices was determined endoscopically and graded I–V as described previously[12]. In addition, they were evaluated by percutaneous or transjugular liver biopsy and visceral angiography. Liver biopsy showed normal hepatic architecture with no evidence of fibrosis or cirrhosis. The venous phase of the angiogram demonstrated thrombosis of the extrahepatic portal vein.

Two methods of injection sclerotherapy were used. In the early part of the study a modified rigid Negus oesophagoscope was used under general anaesthesia and the sclerosant, ethanolamine oleate, injected intravariceally[12]. More recently, sclerotherapy has also been performed via a fibreoptic endoscope under light sedation and a technique of combined intra- and paravariceal injection of ethanolamine oleate used[13].

All patients were assessed and documented prospectively. In the early part of the study patients were injected at one week, one month and then at three-monthly intervals. The present policy is to perform sclerotherapy at weekly intervals until the varices are eradicated and to assess patients at 3 months and then every 12 months. Any recurrent varices are then injected at weekly intervals until eradicated. The mean follow-up period was 45·5 months (range 3–105).

Results

Initial variceal bleed

The first ever variceal bleed occurred before the age of 10 years in 4 patients. These patients had suffered multiple variceal bleeds before entering the study. The majority of the patients ($n = 19$) first presented with variceal bleeding between the ages of 10 and 20 years. The initial variceal bleed occurred between 20 and 30 years in nine patients and after the age of 30 years in seven patients. The older patients had suffered fewer variceal bleeds before entering the study.

Oesophageal variceal bleeding (Table 1)

Before the study period 26 patients had presented with a total of 77 variceal bleeds. Six patients had suffered many bleeding episodes but could not recall the exact number and seven patients were admitted with their first variceal bleed. During the study period, but before eradication of the varices, nine patients were admitted on 13 occasions with bleeding from oesophageal varices. Nine of the thirteen bleeds were of a minor nature and settled on conservative treatment which consisted of a blood transfusion and a continuous intravenous infusion of Pitressin. Four of the bleeding episodes were severe and necessitated the insertion of a Sengstaken–Blakemore tube for the control of bleeding before emergency injection sclerotherapy. Four of the thirty-three patients in whom

Table 1 *Number of variceal bleeds before and after entry into the study*

	No. of patients	No. of previous variceal bleeds
Period before sclerotherapy	26	77
	6	Many
	7	0
Period of sclerotherapy		
Pre-eradication	9	13
Recurrent varices	4	4

Table 2 *Incidence of oesophageal variceal bleeding related to the number of patient months at risk of bleeding before and after entry into the study*

	Before treatment			During treatment		
No. of patients	No. of bleeds	Patient months at risk	Months per bleed	No. of bleeds	Patient months at risk	Months per bleed
17	39	781	20	5	600	120
5	Many	1068	Unknown	3	216	72
7	0	0	0	3	266	88

oesophageal varices had been eradicated suffered a total of four bleeds from recurrent oesophageal varices. Only one patient required a Sengstaken–Blakemore tube for control of bleeding followed by emergency injection sclerotherapy.

Accurate information about previous oesophageal variceal bleeding was available in 29 patients (*Table 2*). The number of bleeds and the number of patient months at risk of bleeding were calculated for two periods: the pretreatment period which extended from the time of the first variceal bleed to the date of entry into the study, and the treatment period which extended from the date of entry to the closure of the study. Seventeen patients had 39 variceal bleeds during 781 patient months at risk before treatment, i.e. 1 bleed per 20 months, compared with 5 bleeds over 600 patient months at risk during the treatment period, i.e. 1 bleed per 120 months. Five patients had suffered many variceal bleeds over a period of 1068 months before commencing sclerotherapy; however they could not recall the exact number of bleeds. During the treatment period of 216 patient months these 5 patients were admitted on three occasions for variceal bleeding (1 bleed per 72 months at risk). The 7 patients who were admitted to the study with their first variceal bleed, had 3 bleeds over 266 months at risk during the study period (1 bleed per 88 months at risk).

Eradication of oesophageal varices

During the 9 year study period, one patient was not referred for long-term repeated sclerotherapy. This patient was included in the control medical management limb of a previous randomized trial[14]. He did, however, receive one acute injection after his initial variceal bleed. He has remained well for 7 years since entering the study and has been hospitalized on four occasions for minor haematemeses which were shown at endoscopy to be due to gastric erosions. The sizes of his oesophageal varices have remained unchanged. Oesophageal varices were eradicated in 33 of the remaining 38 patients. A median number of seven injections (range 1–17) were required over a mean period of 14·5 months (range 1–48) to achieve eradication.

Fewer injections were required to eradicate oesophageal varices in older patients. A median number of eight injections (range 2–17) were needed to eradicate the oesophageal varices in the 18 patients under the age of 20 years whereas four injections (range 1–15) were needed in 15 patients over the age of 20 years ($P < 0\cdot05$, Student's *t* test). The mean variceal grade at the initial endoscopy in the patients under 18 years was $3\cdot72 \pm 0\cdot11$ and in the older patients $3\cdot67 \pm 0\cdot13$.

The oesophageal varices were not eradicated in 5 patients. These patients lived far away and had received between two and eight injections over periods ranging from 9 to 26 months. At the last assessment, the varices were considerably smaller but had not been totally eradicated. One of these patients was admitted with a minor variceal bleed which settled on conservative treatment. All these patients have been difficult to follow-up.

Complications (Table 3)

Complications occurred in 25 patients (64 per cent). These were of a minor nature and included an injection site leak in 5 patients, oesophageal stenosis in 7 and oesophageal slough in 23.

An injection site leak was usually suspected in patients with persistent pain and pyrexia after sclerotherapy, and confirmed on barium swallow. The five patients with this problem all settled on conservative treatment which consisted of nil by mouth, intravenous fluids and antibiotics.

The seven patients who developed a stenosis at the lower end of the oesophagus complained of dysphagia, but only two patients required dilatation for relief of symptoms. All patients were asymptomatic at the end of the study.

Slough at the injection site was noted on follow-up endoscopy on 36 occasions in 23 patients. Occasionally sclerotherapy had to be postponed because of the presence of slough, but in the majority of instances it was not of any significance.

These 48 complications occurred during a total of 250 injections.

Survival

There were no deaths during the 9 year study period, with a follow-up ranging from 3 months to 8·75 years (mean 44 months). Twelve patients were alive more than 5 years after entering the study.

Follow-up after the initial haematemesis in 29 patients ranged from 3 months to 45 years (mean 9·5 years). Nine patients were alive more than 10 years after the initial haematemesis.

Discussion

Extrahepatic portal venous obstruction, although well documented in children, has received little attention as a cause of portal hypertension in adults. However, a significant proportion of patients in recent reports have been adults[5,15]. These studies have unfortunately included other intrahepatic causes of portal hypertension[7–9]. In the present series a non-paediatric group of patients with EHPVO has been studied and the effect of injection sclerotherapy assessed.

Previous reports on EHPVO have also tended to emphasize the value of various surgical procedures, including splenectomy, portosystemic shunts and devascularization operations[10,16]. There is a significant incidence of rebleeding owing to either occlusion of shunts or recurrence of varices after devascularization surgery. Many patients undergo multiple operations for the management of the portal hypertension and these additional procedures are associated with increasing morbidity and mortality. Repeated intra-abdominal operations are also likely to disrupt many of the splanchnic systemic venous collateral channels and thus increase the incidence of rebleeding[7]. A lower mortality has been reported in a non-operated group of patients compared with those treated surgically[5,7].

Of the various surgical procedures, portosystemic shunts, especially distal splenorenal shunts, have given the best results[4,8,10,17]. A problem common to all shunt operations is the effect of diverting the portal flow away from the liver. Portal venous perfusion through collateral channels in patients with EHPVO constitutes a significant part of the total liver blood flow[8,10,18], and loss of this part of the hepatic inflow may predispose to the development of portal systemic encephalopathy[8,18]. The reported incidence of encephalopathy

Table 3 *Complications associated with injection sclerotherapy in 25 patients (64 per cent)*

	No. of patients	No. of complications	Per cent per injection
Injection site leak	5	5	2
Stenosis	7	7	2·8
Slough	23	36	12

following portosystemic shunts, particularly total shunts, in patients with normal livers, although surprising, would support a non-surgical approach in these patients. However, it has been shown that the mesenteric component of the collateral supply is well retained after distal splenorenal shunt in patients with portal vein thrombosis[10].

Surprisingly little data have been published to indicate the natural history of patients with EHPVO, particularly in adults. The long-term prognosis is considerably better than those with portal hypertension due to intrinsic liver disease. These patients appear either to stop bleeding or to bleed less frequently and less severely as they get older[5,7,11]. This is possibly due to new collateral channels opening up as patients get older. Acute variceal bleeding is also well tolerated by these patients because of their normal liver function. Thus, any form of treatment used in the management of portal hypertension in patients with extrahepatic portal venous obstruction should have a low morbidity and virtually no mortality and should be effective in preventing recurrent bleeding. Injection sclerotherapy satisfies many of these requirements. However, its routine use in adult patients with extrahepatic portal venous obstruction has not been documented previously.

In the present study, 39 adult or adolescent patients with extrahepatic portal venous obstruction were treated with injection sclerotherapy. Oesophageal varices were eradicated in 78 per cent of the patients. Fewer injections were needed to eradicate the varices in the older patients even though the sizes of the varices in the two groups were comparable. This is possibly due to the lower pressure in the varices as a result of new collateral channels opening up in older patients. This would also explain the improved prognosis in older patients[5,7,11].

Oesophageal varices were not eradicated in five patients. These patients lived far away and therefore could not attend for frequent sclerosis. Recurrent variceal bleeding was not a problem in these patients. However, surgery may be indicated in patients who live far away and in whom varices are not eradicated by an adequate course of sclerotherapy. Our present policy as a result of the controlled trial[19], is to inject the varices at weekly intervals until eradicated and to assess endoscopically at 3 months and then at 12-monthly intervals.

The incidence and risk of recurrent variceal bleeding both after commencing sclerotherapy and after eradication of varices were significantly reduced. The recurrent bleeds were mostly of a minor nature.

There were no deaths during the 9 year study period. The complications associated with injection sclerotherapy were not a problem and were all treated conservatively. Mucosal slough was usually an incidental finding at follow-up endoscopy. Thus, the significant complications of injection site leak and oesophageal stenosis, occurred in only 10 patients (26 per cent).

The natural history of portal vein thrombosis is varied and unpredictable. The reported good prognosis in these patients was confirmed in the present series. The average duration from the initial variceal bleed to the time of commencing therapy was 7 years (range 1–504 months). There were no deaths in this group of patients with a mean follow-up from the time of the initial variceal bleed of 9·5 years (range 3–541 months). Thus extrahepatic portal venous thrombosis in adult or adolescent patients appears to be a relatively benign disease.

The long-term results of the surgical treatment of patients with portal vein thrombosis have been unsatisfactory. Injection sclerotherapy satisfied most of the requirements of the ideal treatment for these patients. In this series there was no mortality, the morbidity was acceptable and recurrent variceal bleeding was markedly reduced. We therefore recommend that all patients with EHPVO be treated with injection sclerotherapy and that surgery be reserved for patients in whom massive variceal haemorrhage cannot be controlled with sclerotherapy or in whom varices prove difficult to eradicate.

Acknowledgements

Financial support was received from the Medical Research Council of South Africa and from the Staff Research Fund of the University of Cape Town. The Chief Medical Superintendent is thanked for permission to publish patient details.

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Paper accepted 20 December 1986

Br. J. Surg. 1987, Vol. 74, July, 603–606

Prospective randomized trial comparing two injection techniques for sclerosing oesophageal varices: over-tube and free-hand

The safety, efficacy and complications of two techniques of endoscopic injection sclerotherapy were examined in 102 consecutive patients, using either a totally transparent over-tube or the free-hand technique. The choice of treatment was at random. There was a significantly higher control of variceal bleeding when the over-tube technique was used (100 per cent versus *77 per cent,* $P<0{\cdot}05$*). The frequency of re-bleeding before the eradication of oesophageal varices was significantly less in the over-tube group than in the free-hand group* ($P<0{\cdot}01$*), although all re-bleedings were well controlled with additional injections of 5 per cent ethanolamine oleate. There was no significant difference between the two techniques with regard to the frequency of endoscopic injection sclerotherapy for eradication of oesophageal varices. The over-tube technique is safer than the free-hand technique and takes less time to accomplish; at the initial session of treatment, time and bleeding during these techniques were* $11{\cdot}5 \pm 2{\cdot}3$ *min (mean ± s.d.) and* $7{\cdot}3 \pm 5{\cdot}9$ *ml in the over-tube technique, and* $20{\cdot}4 \pm 4{\cdot}1$ *min and* $45{\cdot}1 \pm 30{\cdot}0$ *ml in the free-hand technique* ($P<0{\cdot}001$*, in both time and bleeding).*

Keywords: Sclerosing oesophageal varices, over-tube technique

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Injection sclerotherapy is effective in controlling acute variceal bleeding and in preventing further bleeding from oesophageal varices[1,2]. The survival of patients with bleeding varices is prolonged when repeated injection sclerotherapy is given[3,4].

Prophylactic sclerotherapy is justified because the results of two prospective randomized trials[5,6] showed that prophylactic treatments prolonged the survival time and prevented variceal bleeding in patients with oesophageal varices, when the impending variceal rupture was predicted by oesophageal endoscopy[7].

The major complications of injection sclerotherapy are oesophageal perforation and aspiration pneumonia and some patients have died[8]. Re-bleeding from oesophageal ulcers at the early stage of repeated injection sclerotherapy occurred in 4 per cent[9] to 32 per cent[10] of patients undergoing injection sclerotherapy.

We have long used the so-called free-hand technique in which varices are injected, using a fibreoptic endoscope and a flexible needle. In the early days of our experience with this therapy, one patient died of bleeding from an oesophageal ulcer 2 weeks after endoscopic injection sclerotherapy (EIS) had been performed under unfavourable conditions—namely an unclear view, uncontrollable movement of the oesophagus and respiratory movement[11].

Westaby *et al.*[9] did a prospective randomized study and found that bleeding within the first 24 h of injection was reduced by use of an over-tube and that bleeding-related deaths were also reduced at the expense of increased post-injection pain and one death due to aspiration.

In a prospective randomized trial, we compared the EIS—free-hand and the over-tube techniques—with regard to blood loss, time and volume of the sclerosant at each session of repeated EIS for the eradication of oesophageal varices.

Patients and methods

One hundred and two patients were referred to us for treatment of oesophageal varices, between July 1985 and June 1986. Twenty-three underwent initial injections of the sclerosant during acute variceal bleeding, 35 in elective conditions. Forty-four were given prophylactic injections for blue varices of a moderate size (F2), which occupy less than one-third of the oesophageal lumen and a larger size (F3) which occupy more than one-third of the oesophageal lumen, and showing one of the following: moderately to highly positive red wale marking (an appearance of a wale or whip mark on the variceal surface) and cherry red spots (small red spots on the variceal surface), and haematocystic spot (a large dome-like projection on the surface of large tortuous varices) according to our criteria[7]. On entering the trial, the patients were classified into grades A, B, or C[12].

The patients were randomly allocated (a coin was tossed) to the two groups of 51 each. One patient in each group not given a repeat EIS was excluded for evaluation of the two techniques with regard to bleeding, time, volume of the sclerosant injected, number of injection sessions, weeks for eradication of oesophageal varices and frequency of complications.

The objective, using either technique, was to inject the sclerosant directly into the varix. This injection was initially given 2–3 cm above the gastro-oesophageal junction and the bleeding site. The following injections were carried out up to the 25 cm from the dental arch at 1 week intervals, until all the varices in the oesophagus were eradicated.

We found that in some patients, bleeding occurred at the upper part of the oesophagus. All injections were given to patients under light sedation with intravenous diazepam (5–10 mg) and pentazocine (30 mg), after a topical anaesthesia with 4 per cent Xylocaine, in both techniques.

For the first 24 patients, a Williams sheath[13] was used and for the remaining 27, a transparent over-tube[14] and a modified version of the tube with a second channel for an injection needle (K-S tube, Olympus, Japan, patent pending) was used (*Figure 1*). These over-tubes were used for the initial two sessions of EIS. The following injections were performed with the free-hand technique until eradication of oesophageal varices was attained with repeated injections at 1 week intervals.

The instrument used was the GIF-K series oblique viewing endoscope (Olympus) for the over-tube technique and the GIF-Q series

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Some of these data were presented in poster form at the 87th annual meeting of AGA, May 17–23, 1986, San Francisco

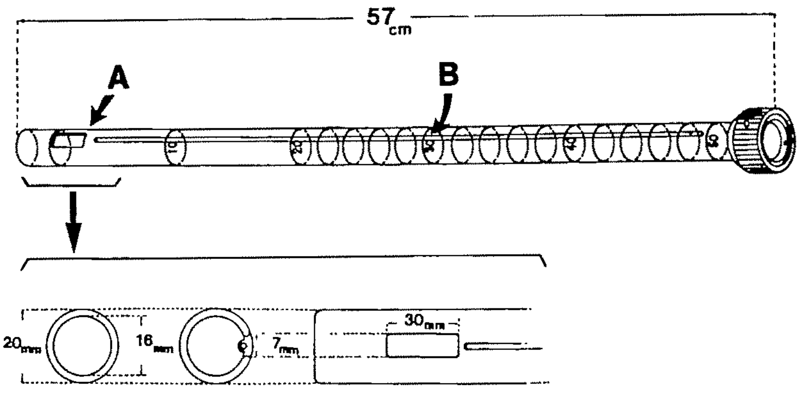

Figure 1 *K–S tube: A transparent over-tube with the slot (A) at the distal end and with the second channel (B) for the injection needle. The injection needle in the second channel is pointed at the varix protruding into the main channel through the slot, while the other compressed varices are visible through the transparent wall*

Table 1 *Clinical data on two groups undergoing sclerosis of oesophageal varices*

	Over-tube	Free-hand
No. of patients	51	51
M:F	38:13	41:10
Mean age	54·4	53·8
Patients with HCC	15	12
Liver disease		
Cirrhosis	49	50
PBC	1	0
CAH	1	1
Child grade[12]		
A	5	8
B	25	27
C	21	16
Occasion of EIS		
Acute	10	13
Elective	25	19
Prophylactic	16	19

HCC, hepatocellular carcinoma; EIS, endoscopic injection sclerotherapy; PBC, primary biliary cirrhosis; CAH, chronic active hepatitis

endview scope for the free-hand technique. The comparative quantities of the sclerosant, 5 per cent ethanolamine oleate, were injected through a flexible needle (Olympus NM3K). The volume of the sclerosant injected was recorded and blood loss during the injection procedures was measured at each session. The time required for injection was also recorded.

To measure blood loss during the procedure, we made use of a glass chamber (100 ml size) between the fibreoptic scope and the main suction chamber. The blood in the oesophagus was collected through a suction channel of the scope during the EIS procedure. When there was a small amount of bleeding, blood loss was estimated by the blood concentrations in the chamber after flushing with 20 ml of saline.

With respect to complications and efficacy, particular attention was directed to post-injection bleeding (requiring blood transfusion), pain, pyrexia (>38°C), oesophageal slough/ulcer, pleural effusion and stricture formation.

The number of sessions and weeks required for eradication of the varices was recorded. Student's t test and χ^2 test was used for statistical analysis.

Results

Characteristics of the two groups

Patients in the two groups were well matched with regard to age, sex, Child's grading and aetiology of liver disease (mainly non-alcoholic liver cirrhosis). There was no significant difference in the clinical condition at the initial treatment between the over-tube and free-hand group (*Table 1*).

Prophylactic injections were given to 16 patients in the over-tube group (7 with F2, 9 with F3 varices) and to 19 in the free-hand group (9 with F2, 10 with F3 varices).

Control of acute bleeding

Control of acute variceal bleeding was obtained in all 23 patients on index bleed (10 in the over-tube and 13 in the free-hand group) with one session of EIS, using an average of 27·5 ml of 5 per cent ethanolamine oleate in the free-hand and 30·5 ml in the over-tube group. In three patients in the free-hand group who continued to bleed from oesophageal varices, despite the injection of more than 20 ml of 5 per cent ethanolamine oleate, the control of bleeding was rapidly obtained with an injection exactly at the bleeding point, under a clear field of vision provided with the over-tube. With the over-tube technique, there was a significantly higher rate ($P<0·05$) of control of variceal bleeding, as compared to the free-hand technique (100 per cent *versus* 77 per cent). We found that this transparent over-tube provides a clearer field of vision during the heavy bleeding from a varix than does the Williams sheath with a black wall, and more rapid and safer injections with the second channel for an injection needle.

Seven patients had an episode of oesophageal bleeding at the early stage of repeated EIS (after one or two sessions). These bleeds were all controlled with one additional session of EIS (6 of 51 in the free-hand and 1 of 51 in the over-tube group).

Eradication of oesophageal varices

Eradication of oesophageal varices was attained in 50 of 51 patients in each group. Two patients did not require a repeat EIS: one in the free-hand group died of hepatoma 1 month after the control of acute bleeding and the other in the over-tube group had a neurological disorder due to cerebral thrombosis 2 weeks after a second session of EIS.

Eradication of oesophageal varices was achieved with 4·1±0·8 injection sessions (mean±s.d.) during 4·8±0·9 weeks in the over-tube group (range 3–6 sessions in 3–7 weeks) and 4·4±0·9 sessions during 5·2±1·2 weeks in the free-hand group (range 3–6 sessions in 4–8 weeks). There was no significant difference in the frequency of repeated EIS between the two groups with regard to eradication of oesophageal varices.

The time required for procedures, the blood loss and volume of the injected solution for both techniques are shown in *Figure 2*.

Blood loss during the procedures for EIS was 7·3±5·9, 5·3±4·3 and 3·36±2·8 ml for the initial, second and third sessions, respectively, in the over-tube group, and 45·1±30·0, 15·8±12·4 and 6·3±5·8 ml in the free-hand group. The over-tube technique produced much less bleeding ($P<0·001$) in the initial and the second session. The time required to complete EIS was 11·5±2·3 (mean±s.d.), 9·6±2·7 and 7·6±2·0 min for the first, second and third sessions of repeated EIS, respectively, in the over-tube group, and 20·4±4·1, 13·2±3·2 and

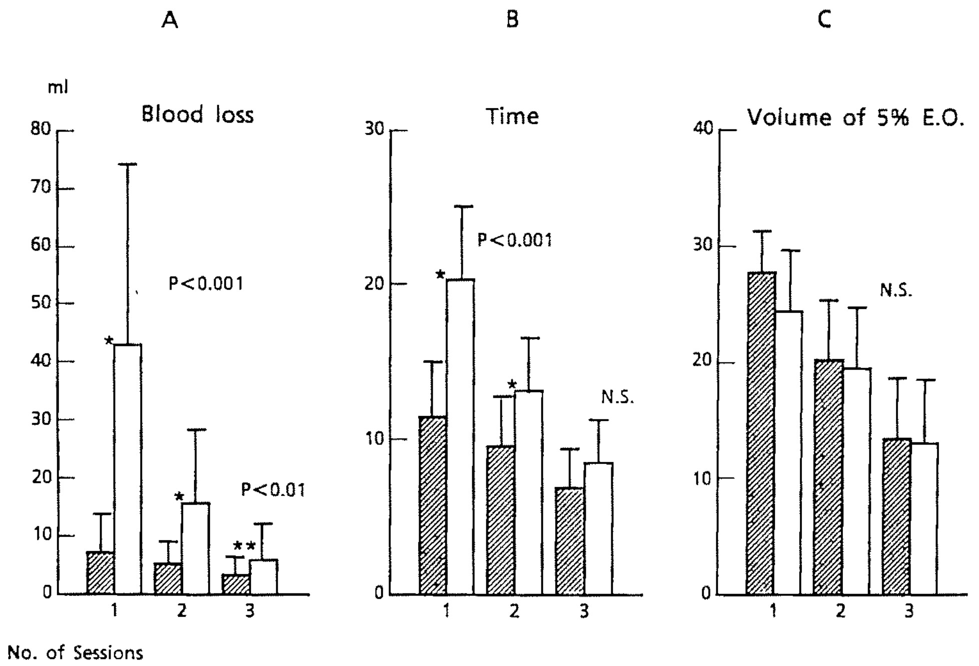

Figure 2 *Blood loss (A), time (B) and volume of the sclerosant (C) injected at each session of EIS.* ■, *over-tube;* □, *free-hand.* * $P<0·001$, ** $P<0·01$. *The over-tube resulted in a significantly lesser extent of bleeding ($P<0·001$ in the initial and second session, $P<0·01$ in the third session of EIS) and required significantly less time ($P<0·001$) in the initial and the second session of EIS than in case of the free-hand technique. There was no statistically significant difference between the two techniques with regard to volume of the sclerosant injected*

Table 2 *Follow-up data*

	Over-tube	Free-hand
Follow-up (months)	2–24	1–24
Late death (at 2 years)	4	6
Survivors (at 2 years)	47	45
Bleeding from varices*	0	0
Recurrence of varices	0	0

* Bleeding after eradication of varices

Table 3 *Bleeds in the early stage of repeated EIS*

Patient	Age	Sex	Child grade	ICG (%)	No. of EIS	Group	Varices
1	54	M	C	60.0	2	OT	E
2	60	M	C	54·8	2	FH	E
3	60	M	C	57·9	1	FH	E
4	69	M	C	35·0	1	FH	E
5	54	M	B	42·5	2	FH	E
6	54	M	C	48·9	1	FH	E
7	55	M	B	32·0	1	FH	E

OT, over-tube; FH, free-hand; E, eradication of varices; ICG, indocyanine green test (normal 0–10 per cent); EIS, endoscopic injection sclerotherapy

Table 4 *Complications of EIS in the two groups*

	Over-tube (%)	Free-hand (%)	P
Pain	32 (64)	30 (60)	n.s.
Pyrexia (>38°C)	29 (58)	31 (62)	n.s.
Early oesophageal ulcer	1 (2)	7 (14)	<0·01
Early bleeding	1 (2)	6 (12)	<0·01
Stricture	5 (10)	3 (6)	n.s.
Pleural effusion	34 (68)	36 (72)	n.s.

8·6±3·1 min in the free-hand group. The over-tube technique required significantly less time than did the free-hand technique ($P<0·001$ in the initial and the second session of EIS). There was no significant difference between these techniques with regard to the volume of the sclerosant injected.

Survival, mortality and bleeding rates

There were no deaths within 30 days after the initial session of EIS, in either group. Survival rate was 92·2 per cent (47/51) in the over-tube group and 88·2 per cent (45/51) in the free-hand group during the 2-year follow-up period. Rate of late mortality during the 2-year follow-up time was 7·8 per cent (4/51) in the over-tube group and 11·8 per cent (6/51) in the free-hand group (*Table 2*).

Bleeding rate was zero in both groups after eradication of the oesophageal varices. To date, varices have not recurred and these patients are being closely followed.

Before eradication of the oesophageal varices, seven patients had a bleeding episode requiring blood transfusion in the early stage of repeated EIS (*Table 3*). One Child grade C patient in the over-tube group with an advanced liver cirrhosis had a bleeding episode 3 days after two sessions. Six patients in the free-hand group had a bleeding episode after one or two sessions of repeated EIS. These seven bleedings were all controlled with further injections and the varices have been eradicated. Thus, early bleeding occurred less frequently in the over-tube group (2 per cent, 1/51) than in the free-hand group (12 per cent, 6/51). There was a statistically significant difference ($P<0·05$) between the two groups. On no occasion was balloon tamponade required for control.

Overall, five of the thirty-seven patients with grade C liver cirrhosis had an episode of recurrent (or initial) bleeding before eradication of the oesophageal varices. This is a significantly higher rate than in patients with cirrhosis in grade A and B categories (1/13 and 2/52, respectively, $P<0·05$).

Complications in the two treatment groups (Table 4)

Post-injection retrosternal pain (requiring opiate analgesics) occurred in 32 of 50 patients (64 per cent) in the over-tube group and 30 of 50 patients (60 per cent) in the free-hand group throughout the treatment. Pyrexia occurred equally in both groups (29 in the over-tube and 31 in the free-hand group). Early oesophageal ulceration occurred in seven and caused oesophageal bleeding in six of fifty patients in the free-hand group at the early stage of repeated EIS, whereas there was only one patient with an episode of bleeding from oesophageal ulcer in the over-tube group. There was a statistically significant difference between the two groups with regard to the incidence of oesophageal ulceration ($P<0{\cdot}01$) and oesophageal bleeding ($P<0{\cdot}01$) at the early stage of repeated EIS.

Symptomatic stricture requiring dilatation occurred after eradication of the oesophageal varices in seven patients (five in the over-tube and three in the free-hand group). Mild pleural effusion was observed on chest X-ray in half the number in each group. Four patients died with no episode of bleeding (two liver failure and two rupture of hepatoma) in the over-tube group. Three patients died of liver failure and three with a hepatoma between 2 and 11 months after the initiation of EIS, with the free-hand technique.

Two patients (one in each group) showed endoscopic evidence of gastric bleeding, a few days before death (one with liver failure in the over-tube and one with hepatoma in the free-hand group).

There were no deaths directly related to variceal bleeding or to the procedures of repeated EIS.

Discussion

The speed and safety with which the sclerosing solution can be injected into varices, in addition to blood loss during the injection procedures, are important factors when evaluating the technique of injection sclerotherapy at each session of EIS. Lai *et al.*[15] reported that with the free-hand technique 8·3 per cent of acute variceal bleeding episodes were not successfully controlled because of blurred vision accompanying massive bleeding and that 11·1 per cent of 108 patients died of variceal bleeding.

The Williams sheath[13] and the transparent over-tube[14] provide a rapid, safer method of sclerosing oesophageal varices and result in a higher rate of control of acute variceal bleeding and less frequent occurrence of early oesophageal ulcer—a possible cause of oesophageal bleeding at the early stage of repeated EIS.

Oesophageal perforation, one of the fatal complications[8,16,17] may reflect a relative inexperience with EIS and seems to occur in those in whom a large volume of sclerosant is given into the deep layer of the oesophageal wall, especially in acute cases where a precise injection is technically difficult. In our series, there were no occurrences of oesophageal perforation attributed to the use of the over-tube, as these tubes provide a clear field of vision and a rapid, safer injection of the sclerosant.

The new transparent over-tube we used provides a much clearer field of vision and seems less traumatic than the Williams sheath, because the wall of the tube is totally transparent and somewhat thicker. Even in patients with acute massive bleeding, the exact point of bleeding is clearly visible through the transparent tube wall and a precise target injection of the sclerosant can be given. At the time of writing, more than 250 patients have swallowed this transparent over-tube, following light sedation and topical anaesthesia.

In accord with the other results[11], there was neither recurrent (or initial) bleeding nor recurrent varix after eradication of oesophageal varices in 100 patients during the follow-up period of 12 to 24 months. However, it is not possible to directly compare our present results with other results[10,18] showing 22 per cent to 36 per cent of recurrent bleeding rates. Oesophageal ulcers are frequently observed at the late stage of repeated EIS and these ulcers produced by repeated EIS, late after thromboses of both main variceal channels and small venous channels located around the varices[19], rarely bleed. These late ulcers and the resulting fibroses prevent the recurrence of varices which originally develop in the mucosal and submucosal layer of the oesophagus. With healing, the mucosal defect is histologically evident[17]. These shallow ulcers seem to be produced at the later stage of repeated EIS by injections of the sclerosant into both thrombosed varices and the residual mucosa of the oesophagus, given to prevent the recurrence of variceal channels in the submucosal layer.

On the basis of this trial, our current policy for repeated EIS is to use the new transparent over-tube technique for the first two sessions of sclerotherapy, to obliterate the variceal channels and minimize the frequency of re-bleeding. Subsequent injections are given using the free-hand technique to eradicate oesophageal varices and hence prevent a recurrent bleeding from the oesophageal varices.

Acknowledgement

We thank M. Ohara, Kyushu University, for critical comments on the manuscript.

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Paper accepted 19 March 1987

Br. J. Surg. 1987, Vol. 74, July,
607–609

New approach in the management of oesophageal varices

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Combined therapy consisting of sclerotherapy, embolization and splenopneumopexy was established for the treatment of oesophageal varices. These procedures were safely performed in 16 patients. No serious complications and no recurrent bleeding have been observed. The varices disappeared or were significantly improved as determined by periodic endoscopic evaluations. Portopulomonary shunt by splenopneumopexy is an alternative technique in the eradication of varices following sclerotheraphy.

Keywords: Sclerotherapy, embolization, splenopneumopexy, oesophageal varices

Wide clinical experience with endoscopic sclerotherapy (ES) has documented its effectiveness in the control of oesophageal variceal bleeding. However, a number of questions remain unanswered[1]. The major unsolved problem linked to sclerotherapy is that the underlying portal hypertension persists and varices often recur[2]. If there are sufficient collateral channels or shunts, recurrence of varices may be prevented and endoscopic sclerotherapy may be more effective. Based upon the experience of portopulmonary shunt by splenopneumopexy[3–5], we have established combined treatment consisting of ES, splenopneumopexy and transcatheter arterial embolization (TAE) of the splenic and left gastric arteries. This paper describes the practical and theoretical implications of these procedures.

Patients and methods

Between December 1983 and March 1986, 16 consecutive patients with oesophageal varices were treated (*Table 1*). The diagnosis was based on histology obtained by percutaneous needle biopsy or intraoperative liver biopsy. Three of the sixteen patients were HBs-antigen positive. Seven patients used to drink 0·5–1 litre of rice wine per day, but were not considered excessive drinkers. Moderate ascites was present in four patients. The mean wedged hepatic venous pressure was 278·8 ± 63·4 mm saline and free hepatic venous pressure was 94·8 ± 71·2 mm saline. Mean splenic pulp pressure was 291·2 ± 48·2 mm saline.

Six patients were classified as Child's A, seven as Child's B and three as Child's C. In the Child's C group, two had ascites with poor nutritional status and the other, the oldest patient, had chronic encephalopathy with a spontaneous splenorenal shunt and moderate ascites.

Technique

Endoscopic sclerotherapy. Sclerotherapy was performed under fluoroscopy in an X-ray room in order to determine the accuracy of the intravariceal injection and perform angiograms. Using standard sedation (intravenous pentazocine and/or diazepam), intravariceal injection of 5 per cent ethanolamine oleate was achieved with a flexible endoscope (Olympus EF-B3) adapted with a proximal balloon, similar to that described by Sievert *et al.*[6]. Intravariceal injection was continued by injecting 5 ml of contrast medium under fluoroscopy before injecting the sclerosant. For each intravariceal injection, 10 ml of sclerosant was used, and the maximum volume of sclerosant at the initial sclerosis was 30 ml.

Transcatheter arterial embolization (TAE). Using the Seldinger technique, a precurved KIFA Red catheter (AB company: Sweden) was introduced into the splenic artery and the left gastric artery. The splenic artery was occluded with Gianturco's coils. Two or three coils 3 mm in diameter were introduced into the distal branches in the splenic hilum and coils 5–8 mm in diameter were led into the mid-splenic artery. The left gastric artery was occluded by embolization with Spongel (Yamanouchi Pharm. Co., Japan) divided into small pieces and soaked in normal saline solution.

Splenopneumopexy. A left lateral thoracotomy was performed through the eighth intercostal space, beginning in the left anterior axillary line and extending to the left mid-scapular line.

A circle, 7 cm in diameter, was mapped out lateral to the tendinous centre of the diaphragm. A small incision was made in the diaphragm which was then excised at the marked line by sequential clamping and division.

The cut edge of the diaphragm was fixed to the upper portion of the spleen with a single row of 3-0 Vicryl sutures. The suture was first passed through the cut edge of the diaphragm into the spleen to some depth, returned to pass through the diaphragm, and then tied tightly. If the stitch into the spleen is too shallow, laceration and bleeding occur on tying. Bleeding can be easily controlled by compression with a wet sponge. This procedure was performed around the cut margin of the diaphragm, so that as much as possible of the exposed area of the spleen was placed in the thoracic cavity.

Multiple rectangular shallow incisions were made in the capsule of the exposed spleen (*Figure 1*). The splenic capsule with the visceral peritoneum overlying it was peeled away carefully with right-angle forceps. Oozing from the abraded surface of the spleen was controlled by compression with a sponge soaked with warmed saline. TAE of the splenic artery contributes considerably to reducing such haemorrhage.

The diaphragmatic surface of the visceral pleura in the inferior lobe of the left lung was then abraded with a rasp to produce capillary bleeding and minor air leakage.

The spleen was fixed to the lung with 3-0 Vicryl sutures. Several sutures were placed to fix the decapsulated spleen to the abraded lung. The needle was placed deeply into the decapsulated spleen to prevent

Table 1 *Clinical and biochemical data in patients undergoing sclerotherapy and splenopneumopexy*

Number of patients	16
Sex (M:F)	8·8
Age (years)	57·3 ± 6·6
Liver disease	
Cirrhosis	13
Posthepatitic	9
Alcoholic	2
Chronic active	2
Idiopathic portal hypertension	3
Liver function	
Bilirubin (μM/l)	13·7 ± 5·1
Albumin (g/l)	34 ± 5
SGOT (units/l)	41·8 ± 12·9
Alkaline phosphatase (KAU/l)	10·7 ± 2·9
ICG R_{15} (%)	30·8 ± 19·1
Ascites	
Moderate	4/16 (25·0%)
Encephalopathy	
Moderate	1/16 (6·3%)
Child's criteria	A:6, B:7, C:3

KAU, King–Armstrong units

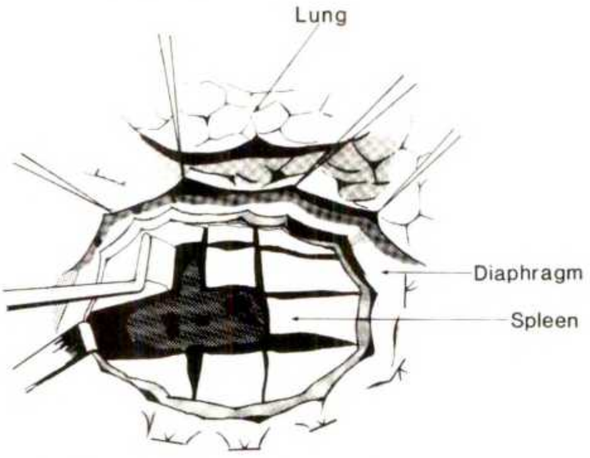

Figure 1 *Dissection of the splenic capsule*

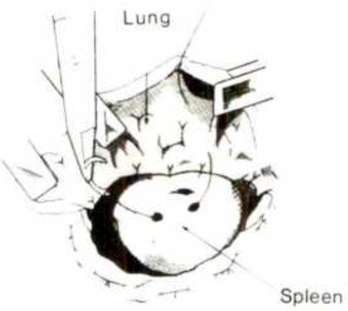

Figure 2 *Fixation between the spleen and the lung*

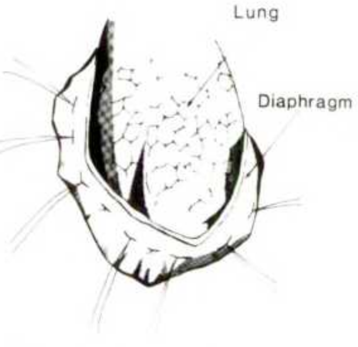

Figure 3 *Completion of splenopneumopexy*

laceration after tying (*Figure 2*). At the margin of the excised diaphragm, the edge of the lung was placed well beneath the diaphragm to avoid dead space between the spleen and the lung. Minor bleeding from the sutured portion of the spleen is normally arrested when the splenopneumopexy is complete (*Figure 3*).

The thoracic wound was closed and a tube placed in the thoracic cavity.

Effective collateral vascular communications between the splenic vein and pulmonary vein can generally be expected within 1 month following splenopneumopexy (*Figure 4*).

Sclerotherapy was the first choice for patients with actual variceal bleeding. One week later, endoscopic examination was carried out, and further injections were performed if there were patent varices. One to two weeks after the first injection, TAE of the splenic and left gastric arteries was carried out, with angiographic evaluation of the portal system. When platelet counts increased after splenic artery embolization, splenopneumopexy was performed. Usually 2–3 weeks were required for platelet counts to increase to their maximum level. However, thrombocytopenia is not in itself a contra-indication for elective splenopneumopexy.

Follow-up endoscopy was performed periodically at intervals of 1 or 2 months.

Results

Sclerotherapy arrested haemorrhage in the five patients bleeding actively at the time of endoscopy. Endoscopy revealed a 'red colour sign'[7] in all 16 patients. ES was performed an average of $2{\cdot}5 \pm 1{\cdot}0$ times.

Mean platelet counts increased from 69 ± 22 to $156 \pm 112 \times 10^9$/l within 2 weeks of TAE of the splenic and left gastric arteries. Maximum elevation was noted 2 weeks after TAE; the platelet counts then fell gradually, although the value at 4 weeks remained higher than the initial value. No significant changes in liver function tests were observed after TAE of the splenic and left gastric arteries.

Portopulmonary shunt by splenopneumopexy was performed at approximately 2–3 weeks after TAE or ES. The estimated blood loss during surgery ranged from 70 to 1120 ml, with an average of 352 ml. The operation time was 150–250 min, and averaged 178 min. No serious haemorrhage or other complications occurred.

The follow-up period was a maximum of 29 months with recurrence of varices seen in only one patient at scheduled follow-up endoscopy. Recurrent bleeding did not occur. One patient died of hepatic failure 4 months after surgery. Oesophageal varices with a 'red colour sign' either disappeared or improved significantly at periodic endoscopic examination.

Complications

Endoscopic sclerotherapy. Transient chest pain was experienced by 57 per cent of the patients. Ulceration of the oesophagus occurred in almost half of the patients. They were placed on antiulcer drugs and all ulcers healed within 2–3 weeks. Transient haematuria and pleural effusion occurred in 12 per cent of the patients.

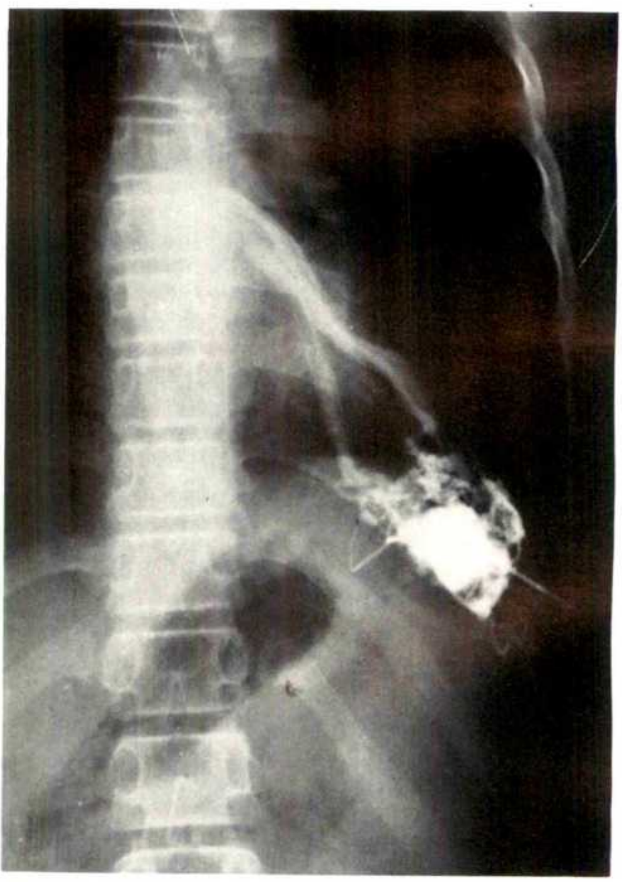

Figure 4 *Visualization of portopulmonary shunt by splenoportography after splenopneumopexy showing the large collaterals draining into the pulmonary veins*

Transcatheter arterial embolization of the splenic artery and the left gastric artery. Fever and abdominal pain were observed in most patients. These symptoms resolved in 2–3 days and were treated by intravenous hydrocortisone (100 mg/day). Partial splenic infarctions were observed in the majority of patients but periodic ultrasonography or computed tomography showed spontaneous reduction in the infarcted area within 2–3 weeks.

Splenopneumopexy. Pleural effusion and ascites occurred in 2 of the 16 patients after surgery, but were easily controlled by diuretics. No postoperative respiratory, cardiac and infective complications were encountered. Haemoptysis was observed in some patients, but it resolved spontaneously within a few days of the operation. None of the patients developed hepatic failure and recurrent bleeding.

Haemorrhage from the thoracic drainage tube usually amounted to 200–500 ml in the 2–3 days after surgery. All patients were discharged in a satisfactory condition within 2 weeks of the operation, and had returned to normal activity by the time of follow-up.

Discussion

Sclerotherapy is currently the most popular form of therapy for oesophageal variceal bleeding, although recurrence is common. According to Terblanche[2], repeated sclerotherapy is recommended for recurrent varices, yet this approach increases the likelihood of complications such as oesophageal stricture and mucosal slough. According to one report[8], sclerotherapy reduced the recurrence of varices in patients who developed new and/or enlarged collaterals, and was accompanied by a decrease in portal pressure. Thus, any additional shunting may improve the efficacy of sclerotherapy, but the surgical procedures must be technically simple and safe since the majority of these patients are cirrhotic. Our experience suggests portopulmonary shunt by splenopneumopexy is a reasonable shunt procedure which facilitates natural collateral formation[3–5].

Conventional splenopneumopexy is divided into an abdominal phase and a thoracic phase. Devascularization of the abdominal oesophagus and the proximal stomach accompanied by ligation of the splenic artery is carried out in the abdominal phase. Currently, non-operative procedures can replace operative splenic artery ligation and devascularization, since occlusion of the splenic artery can be achieved by interventional angiography and endoscopic devascularization can be accompanied by sclerotherapy.

A hyperdynamic splenic circulation associated with splenomegaly and hypersplenism occurs in patients with portal hypertension[9]. Splenic artery occlusion is accompanied by a decrease in portal pressure, an increase in the diameter of the hepatic artery and a decrease in the diameter of the portal vein. This suggests an increased hepatic blood flow which correlates with improved hepatic function[10]. Splenic parenchymatous embolization with gelatin sponge induces subtotal infarction of the spleen, and has been used to treat hypersplenism[11]. Widespread splenic infarction does not favour shunting by splenopneumopexy. Even using coils for embolization, segmental infarction of the spleen cannot be avoided. From our experience, this resolves within 2–3 weeks without infection and abscess formation. Periodic ultrasonography and computed tomography examinations are required to follow resolution. Our objectives in splenic embolization are to reduce blood loss during splenopneumopexy, and improve the platelet count. In addition, the left gastric artery is embolized as it contributes to the oesophageal varices through the submucosal arteriovenous anastomosis in the oesophagogastric area[12]. Thus, the effects of this combination therapy can be explained as follows: (1) intravariceal sclerotherapy leads to endoscopic devascularization; (2) portopulmonary shunt by splenopneumopexy facilitates effective collateral formation; (3) TAE of the splenic artery and left gastric artery favours safe splenopneumopexy and eliminates factors contributing to portal hypertension, oesophageal varices, and hypersplenism.

ES or TAE is our first choice of treatment for most patients. Splenopneumopexy should be performed after TAE of the splenic artery. The correct timing of splenopneumopexy remains to be determined, but should certainly be deferred until 'red colour sign' of varices and thrombocytopenia have been treated by ES and TAE.

The intra-operative and postoperative course in our patients was smoother than is usual following major abdominal surgery for oesophageal varices, and average blood loss and operation time were acceptable. During the follow-up period, the oldest woman died of hepatic failure 4 months after the operation. She had hepatic encephalopathy with spontaneous splenorenal shunt prior to surgery. At present, candidates for splenopneumopexy are limited to those without obvious jaundice, encephalopathy or spontaneous shunt, and to those who have a spleen of normal size.

Although the follow-up period was too short for assessment of definite results, the surviving 15 patients are well and free from recurrent bleeding and encephalopathy. The varices have disappeared or are significantly improved. In conclusion, splenopneumopexy is an additional procedure which may resolve some of the problems associated with sclerotherapy. It is safe, simple and effective.

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Paper accepted 4 March 1987

Br. J. Surg. 1987, Vol. 74, July, 610–611

Balloon tamponade for the control of Mallory–Weiss haemorrhage in patients with coagulation defects

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Patients with Mallory–Weiss syndrome comprise between 5 and 15 per cent of all patients with upper gastrointestinal haemorrhage[1]. The association with excessive alcohol consumption and hiatus hernia is now well recognized. The mucosal tear is usually superficial and most patients can be successfully managed conservatively[2]. Patients who continue to bleed include those with a coagulation defect secondary to liver disease. In the past surgery was often used as a last resort to control bleeding.

We report the use of balloon tamponade in six patients with the Mallory–Weiss syndrome, where there was severe continuing haemorrhage associated with a coagulation defect as a consequence of liver disease.

Methods and results

Six patients with the Mallory–Weiss syndrome, in whom conservative measures failed to control bleeding, were referred during a 1 year period. The patients (*Table 1*) were aged between 28 and 85 years. In five patients an episode of heavy drinking had preceded the event. All six patients had liver disease with evidence of a coagulation defect.

The mean prothrombin time in these patients was 22 s (range 19–24; normal value 12–15), the mean kaolin cephalin clotting time was 57 s (range 54–61; normal value 36–50), the mean thrombin time was 11 s (range 9–12; normal value 6–9) and the average platelet count was 86×10^9/l (range 78–97).

At endoscopy gastro-oesophageal mucosal tears with active bleeding were found in all patients. The tears were single in five patients and one patient had two tears. In four patients the tear involved the lesser curve side of the stomach, and in each extended into the oesophagus. In two patients the tear was on the greater curve of the stomach, extending into the oesophagus, with one of these patients also having a posterior gastro-oesophageal tear. The average length of the tear was 3 cm (range 2–4). In addition, all six patients had hiatus hernias.

The initial management consisted of volume replacement, fresh frozen plasma and cryoprecipitate. Mean transfusion requirement was 5·8 litres before tube insertion. Immediate control of haemorrhage was achieved in all six patients by the pernasal passage of a Minnesota tube with inflation of both gastric and oesophageal balloons. The oesophageal balloon pressure was maintained at 40 mmHg for 24 h and then deflated. The tube was removed 2–3 h later and there was no evidence of further haemorrhage in any patient. In all six patients there was improvement in the coagulation abnormalities during the 24 h of balloon tamponade, but in none had coagulation returned to normal.

Discussion

Various non-surgical methods have been employed to control haemorrhage in patients with the Mallory–Weiss syndrome. Bubrick *et al.*[3] routinely used systemic vasopressin, but eight of their fifty-nine patients underwent surgery. Fisher *et al.*[4] reported control of haemorrhage in eight of thirteen patients treated with coeliac or left gastric artery infusion of vasopressin. Gelatin sponge embolization of the left gastric artery controlled bleeding in three of the five patients reported by Carsen *et al.*[5]. Endoscopic electrocoagulation was successful in nine of the ten patients who continued to bleed in the series reported by Sugawa *et al.*[1].

The use of balloon tamponade is controversial. Critics of the technique have argued that balloon tamponade is of no value in the presence of hiatus hernia as the mucosal tears are usually confined to the herniated portion of the stomach[3,6]. Balloon tamponade of 40 mmHg will not control haemorrhage if it is arterial and this may account for the failure of tamponade to control haemorrhage as reported by Sugawa *et al.*[1] and Hastings *et al.*[7]. In patients with hiatus hernia failure due to incomplete tamponade of the herniated portion of the stomach may occur[8]. The mucosal tear extended across the gastro-oesophageal junction in each of our patients; permitting compression with both oesophageal and gastric balloons, and the presence of the hiatus hernia did not result in incomplete tamponade. Another possible problem is the risk of further mucosal tears occurring in the herniated portion of the stomach but this was not a problem in any of the patients presented. Conversion of a partial thickness laceration into a full thickness tear has not, to our knowledge, been reported.

Although the coagulation abnormalities improved in all our patients after infusion of fresh frozen plasma and cryoprecipitate in none were the abnormalities completely reversed. This suggests that the tamponade was primarily responsible for stopping haemorrhage. In patients with continuing haemorrhage from the Mallory–Weiss syndrome, associated with coagulation abnormalities due to underlying liver disease, balloon tamponade is a simple and safe procedure to control bleeding.

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Table 1 *Patients' details*

Patient	M/F	Age	Alcohol related event	Liver disease	Coagulation defect	Transfusion requirements (litre) before tamponade
1	F	34	Yes	Alcoholic hepatitis	Present	4
2	F	28	Yes	Alcoholic hepatitis	Present	3
3	M	54	Yes	Alcoholic cirrhosis	Present	5
4	M	55	Yes	Alcoholic cirrhosis	Present	10
5	F	75	No	Cryptogenic cirrhosis	Present	6
6	M	55	Yes	Alcoholic cirrhosis	Present	7

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Paper accepted 16 January 1987

Br. J. Surg. 1987, Vol. 74, July, 611–612

Use of ultrasound scan as a bedside diagnostic aid

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Ultrasound scanning (US) is invaluable in many surgical patients because of its high accuracy, non-invasiveness and the ease with which it can be performed[1,2]. Since increasing demands on our ultrasound department can result in delays in obtaining urgent and routine scans we investigated the feasibility, accuracy and time-saving potential of immediate bedside scanning performed by surgeons in training.

Patients and methods

Before commencing the study the participating surgeons (one senior and three junior registrars) underwent a period of training. This consisted of one lecture and demonstration by a consultant radiologist on the technique of scanning and the interpretation of results; this was followed by 6 weeks of unsupervised practical experience in bedside scanning. Each participant spent about one hour per week scanning. Initially, patients with known pathology were used for familiarization. These findings were recorded for appraisal and not used in the results.

Over a subsequent 9 month period we studied patients presenting to Walton Hospital with acute abdominal pain. The criteria for selection was based on clinical judgement and the knowledge of the merits of US as a diagnostic tool. All patients with upper abdominal symptoms suggestive of hepatobiliary and renal pathology and those with abdominal masses were included in the study. Clinically obvious diagnoses in which US is not known to be useful, such as appendicitis or intestinal obstruction, were excluded.

The US scanner used by the surgeons was a Toshiba Sonolayer L 5AL 22A whilst that used in the radiology department was an ATL MK 100. Scans were performed and recorded at the bedside within 24 h of admission by the duty surgeon. At the same time a standard request was made for a separate scan to be done in the radiology department. The surgeon assessed whether the US findings assisted him in his decision either to avoid surgery, to reaffirm the choice of non-operative treatment or to strengthen the decision to operate. The surgeons' US findings were compared with those of the radiologist and compared with the definitive diagnoses obtained from further investigations or at subsequent surgery.

The scans were categorized into either correct, false positive or false negative. Dates of admission and discharge for each patient were recorded. The extra time in hospital awaiting scans was calculated from the date when each patient was considered clinically fit for discharge.

Table 1 *Overall diagnostic accuracy between surgeons and radiologist*

	Correct	False positive	False negative	Incorrect %
Surgeons	65	6	0	9·2
Radiologist	68	2	1	4·4

$n = 71$, $\chi^2 = 1·07$, $P < 0·1$

Results

Seventy-one patients had US scans performed by the surgeons and radiologist. The definitive pathology in 57 (80.3 per cent) patients was hepatobiliary, namely: cholelithiasis, gallstone pancreatitis or secondary liver disease. There were 2 (2·8 per cent) cases each of abdominal aortic aneurysms, pyelonephritis and early pregnancy. The 8 (11·3 per cent) remaining cases were gastric ulcer, diverticulitis, ascites, adhesions, hydronephrosis, salpingitis, diabetes and skeletal pain. Surgeons and radiologist were correct in 65 (91·5 per cent) and 68 (95·7 per cent) of the cases respectively (*Table 1*). When only the patients with hepatobiliary diseases were considered, surgeons and radiologist achieved 53 (93·0 per cent) and 56 (98·2 per cent) correct scans respectively. There was no significant difference between the two groups ($\chi^2 = 1.07$, $P < 0·1$). Scans by the radiologist were done 1–16 (mean, 4·7) days after admission. The total extra time spent in the hospital awaiting a radiological scan was 64 days for 71 patients (range, 0–10; mean, 0·9 days per patient).

In 25 (35·2 per cent) patients the clinical management was influenced by the results of bedside US scanning. In 12 (16·9 per cent) of these correct early scans helped to avoid unnecessary laparotomy. Conservative treatment was reaffirmed in 10 (14·1 per cent) patients. In three (4·2 per cent) patients (one small leaking aortic aneurysm, one bleeding peptic ulcer and one pelvic inflammatory disease) immediate scanning strengthened the decision to operate by excluding a diagnosis of biliary disease. In 46 (64·8 per cent) patients the clinical management was not influenced by bedside US scans.

In 4 (5·6 per cent) patients surgeons made equivocal but false diagnoses of gallstones which were subsequently corrected by the radiologist. Both misdiagnosed two patients with salpingitis and ovarian tumour for diverticulitis. No patient had unnecessary operation as a result of this.

Discussion

Heavy demands for ultrasound scans inevitably lead to delays in obtaining early diagnosis. In many Merseyside hospitals elderly dependent patients who are otherwise fit for discharge are often given the option to stay in hospital in order to keep their US appointment. If the patients in our trial had been allowed to be discharged when they were fit enough, there would have been a reduction in hospital stay of almost one day per patient, i.e. a potential saving of 64 in-patient days over a period of 9 months.

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The diagnostic accuracy of the consultant radiologist and the surgeons in training are surprisingly comparable. We attribute this high competence to the surgeons' detailed knowledge of the clinicopathological anatomy.

The US scanner used by the surgeons is a basic model compared with the sophisticated machine available to the radiologist. With more training, better equipment and careful selection of patients, surgeons might further improve their accuracy rate. Our twelve patients who had acute cholecystitis or pancreatitis were clinically undistinguishable from perforated peptic ulcer using conventional investigation. Laparotomy might have been advised. The immediate visualization by US of a calculus within a tender thickened gallbladder eliminated the need for emergency surgery. Where a clinical decision to operate is already made, US scan is of academic interest but a firm preoperative diagnosis such as a small leaking aneurysm is reassuring to the duty surgeon. Our radiology department sees no reason why adequately experienced surgeons should not perform and act upon US scans themselves, much as they already do with plain radiography of the abdomen. Equivocal bedside scans should be repeated by the radiologist in his department in order to avoid false positive results.

We recommend that US scanning should form part of the training of general surgeons whose use of this facility might be analogous to the physician's use of the electrocardiogram.

Acknowledgement

We thank Mr S. Tong for his contribution to the concept of this project.

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Paper accepted 9 October 1986

Surgical workshops

Br. J. Surg. 1987, Vol. 74, July, 612–613

Modified hepaticojejunostomy for permanent biliary access

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Complex intrahepatic strictures, recurrent biliary calculi and sclerosing cholangitis pose major technical problems which may be complicated by limited or difficult surgical access. Permanent access hepaticojejunostomy provides a method for repeated percutaneous stricture dilatation or stone extraction. We

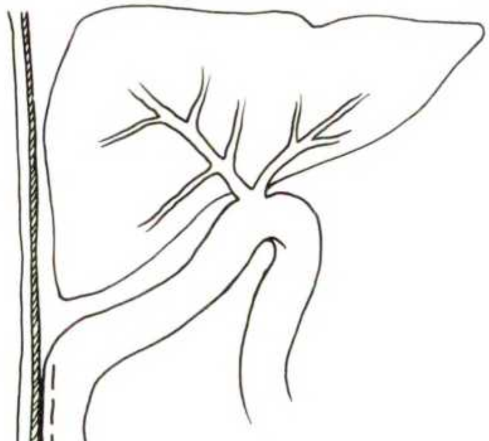

Figure 1 *Diagram of Roux-en-Y hepaticojejunostomy with percutaneous access loop attached to anterior abdominal wall*

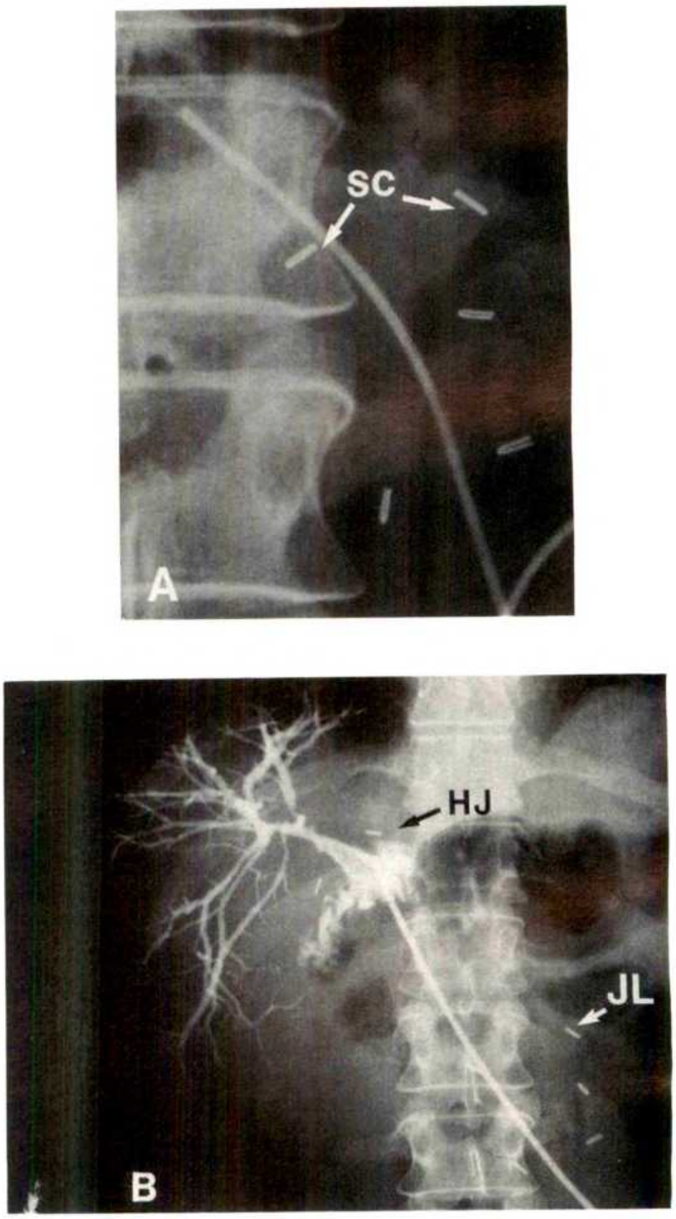

Figure 2 *Silver clips (SC) guide percutaneous catheter entry into the jejunal loop (JL) and hepaticojejunostomy (HJ)*

describe a modified hepaticojejunostomy technique which avoids the disadvantages of either a cutaneous stoma, external stenting or subcutaneous placement of the jejunal loop.

A retrocolic Roux-en-Y jejunal loop is anastomosed side-to-side at the hepatic duct bifurcation 15 cm proximal to the closed end of the jejunal loop. Two silver clips mark the anastomosis for later radiological identification. The closed proximal limb is attached to the fascia and peritoneum of the anterior abdominal wall over a distance of 6 cm (*Figure 1*). The width of the attached bowel is marked with a parallel row of silver clips (*Figure 2A*). The afferent jejunal limb should be short to prevent kinking and to allow linear access to the intrahepatic biliary system.

Local anaesthetic is infiltrated at the puncture site. The afferent jejunal loop is identified by 23 gauge fine needle contrast injection, guided by the parallel row of silver clips. Percutaneous introduction of a larger 18 gauge needle-catheter combination, directed fluoroscopically into the bowel lumen, provides radiological access. A biliary guidewire locates the intrahepatic duct system and a 7 French arterial catheter and Gruntzig balloon catheter allow intrahepatic cholangiography (*Figure 2B*) and therapeutic intervention. This technique permits safe and reliable permanent biliary access without bile leakage, local sepsis or permanent stenting.

Paper accepted 9 January 1987

Br. J. Surg. 1987, Vol. 74, July, 613

Operative choledochoscopy via the cystic duct: a pilot study with an ultra-thin fibreoptic endoscope

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The detection of stones in the bile ducts during cholecystectomy is clearly of importance. At present most surgeons use peroperative cholangiography and this approach reduces the retained stone rate to less than 5 per cent and yields unsuspected common bile duct stones in about 5 per cent of patients[1,2].

Operative cholangiography is time consuming, is sometimes technically unsatisfactory and involves radiation exposure to both patient and operating theatre personnel. Despite the use of intra-operative cholangiography negative exploration of the bile duct occurs in up to a third of explorations[3]. Choledochoscopy of the bile ducts is a well established technique during common bile duct exploration using either rigid or flexible fibreoptic instruments[4]. We describe our initial experiences with a prototype ultra-thin choledochoscope.

Procedure

An ultra-thin fibreoptic endoscope (Olympus P.F.) with an external diameter of 2·5 mm and a channel diameter of 0·5 mm was investigated during cholecystectomy in 10 patients. The instrument was sterilized by ethylene oxide gas. A standard two-film cholangiogram was done by passing a ureteric catheter via the cystic duct and injecting 3 and another 5 ml of contrast (Conray 280). Following inspection of the radiographs the cannula was removed and the choledochoscope passed via the cystic duct into the bile duct. It was sometimes necessary to pass a probe or to make a longitudinal incision in the cystic duct to facilitate the passage of the endoscope. The duodenum was not mobilized routinely. The endoscope has no directional control but its direction was controlled within the bile duct by holding it between a finger and thumb on the outside of the duct. It was found difficult to infuse saline fast enough to distend the ducts and achieve a good view: latterly distension with air was used.

It was possible to introduce the instrument into the common bile duct via the cystic duct in 9 of 10 patients; in the remaining patient the cystic duct was very narrow and fibrosed. In the remaining nine patients good views were obtained which were certainly comparable with a conventional fibreoptic choledochoscope. The distal common bile duct was clearly seen and it was possible to pass the endoscope through the ampulla into the duodenum. The procedure took ≈ 10 min to perform. Views of the common hepatic and intrahepatic biliary tree were only achieved in five patients, because of angulation at the cystic duct/common duct junction. No complications occurred either during or following the operation.

Discussion

We describe the use of an ultra-thin (2·5 mm) flexible fibreoptic choledochoscope for choledochoscopy via the cystic duct. The quality of views obtained were very good; inserting the endoscope was seldom a problem. Gas was preferable to fluid for distending the duct, CO_2 being better than air because of the possible risk of embolism. The smaller diameter of this instrument allows it to be passed through the ampulla into the duodenum. The practical value of this instrument is as yet uncertain; modifications to allow it to be sterilized by immersion and to give it a larger channel diameter for fluid infusion would be useful but the external diameter is also important and the prototype instrument is certainly useable. The instrument is at present very fragile and would probably not survive routine use. A shorter, stiffer endoscope would be required. Ultra-thin choledochoscopy via the cystic duct may be a useful alternative to cholangiography, and its use before exploration of the bile duct may reduce the negative exploration rate still found using operative cholangiography. The ultra-thin choledochoscope requires further evaluation, but initial experience suggests that this evaluation will be worthwhile.

Acknowledgement

We are grateful to Olympus for the loan of the ultra-thin endoscope.

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Paper accepted 30 November 1986

Br. J. Surg. 1987, Vol. 74, July,
614–617

Treatment of postoperative gastrointestinal atony

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One hundred and eighteen patients in whom postoperative gastrointestinal atony had lasted for 48–72 hours, were given one or two intravenous injections of different doses of cisapride (2, 4 or 8 mg), or vehicle. The first occurrence of flatus was taken to mark the cessation of ileus. There was no significant difference in remission of ileus between the groups in the first hour following injection. All patients not responding to treatment in the first hour were given a repeat dosage and observed for the following 3 hours. Among this group, there was a significant remission of ileus in patients who had received 2 × 8 mg, which was particularly marked in those who had undergone intraperitoneal surgery. This study suggests that cisapride in repeated dosage may be of value in inducing remission in prolonged surgical ileus, particularly in patients who have undergone intraperitoneal operations.

Keywords: Cholinergic nerves, cisapride, flatus, postoperative ileus, propulsive peristalsis

Postoperative gastrointestinal atony, a phenomenon observed after virtually all surgical interventions, may cause considerable discomfort to the patient. Generally, the motility of the entire gastrointestinal tract is inhibited after the operation and recovery occurs gradually from the stomach to the rectosigmoid[1,2]. The stomach resumes its activity first[1], although a delay in gastric emptying of undigestible solids may be observed up to 48 hours after operation[3]. Postoperative inhibition of gastric evacuation for 12–24 h has also been demonstrated in animal models[4].

Small bowel electrical and contractile activity returns quickly (i.e. within 7 h) after the restoration of gastric motility[1]. However, the real site of the ileus seems to be the left colon[1,2]. In monkeys, inhibition of segmental or propulsive contractions was shown to be most profound in the sigmoid colon, where it lasted up to 72 hours, against approximately 24 h in the right colon[2]. Activity in the right colon in humans is suppressed for about 16 h after extra-abdominal operations and for 40–48 h after intra-abdominal surgery as measured by single-site registration of intraluminal pressure[5].

Cisapride(cis-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy) propyl]3methoxy-4-pyperidinyl]-2methoxybenzamide.monohydrate) is a new pharmacological agent, developed by Janssen Pharmaceuticals[6]. It selectively enhances acetylcholine release from the postganglionic cholinergic nerve endings in the myenteric plexus[7,8]. It does not bind to muscarinic or dopamine receptors[9]. *In vitro* and *in vivo* it furthers spontaneous phasic contractions in stomach and duodenum of dogs, while lowering their mean frequency[10,11]. It improves coordination of antral and duodenal contractions leading to acceleration of gastric emptying[10,11].

In the interdigestive state, an intravenous injection of cisapride immediately induces a burst of strong, regular contractions resembling phase III of the migrating motor complex in the small intestine of the dog[10,12,13]; in the postprandial state, cisapride also increases propagation of spike bursts[10,14,15].

In an isolated guinea-pig colon preparation, cisapride induces concentration-dependent contractions of the longitudinal muscle, causing fluid displacement[7,9] and in the dog, transit of markers in the colon is accelerated[12]. This effect may not be due to enhancement of acetylcholine release but to some other, as yet unknown, mechanism[7,9].

The aim of this clinical study was to try to overcome postoperative gastrointestinal atony by direct stimulation of the excitatory nerves in the myenteric plexus, using cisapride.

Patients and methods

Patients were entered to the trial if postoperative atony (auscultatory silence, no flatus, no stools) had lasted between 48 and 72 h, irrespective of the type of surgery. One hundred and eighteen adult patients were studied (*Table 1*). The patients were randomly assigned to double-blind treatment with either 0 mg (solvent only), 2 mg, 4 mg or 8 mg of cisapride. The selection of this dose range was based on a small-scale trial suggesting that 4 mg was active. The medication was given in a slow (2 mins) direct intravenous injection and not through an already connected intravenous line since cisapride is incompatible with some infusion liquids, i.e. those containing high concentrations of electrolytes. If no flatus was observed within one hour after the first injection, the same intravenous dose was repeated. Rectal cannulae were not applied. Treatment with parasympathetic drugs (e.g. neostigmine, bethanechol), sympathicolytics (e.g. trifluperidol, chlorpromazine) or gastrokinetics (metoclopramide, domperidone) was not allowed during the study.

The end point of the study was the occurrence of distinct flatus. Patients were observed for one hour after the first injection and, hourly for 3 h after the second.

The results were stratified according to the type of intervention because resumption of propulsive bowel motility as well as the expulsion of gastrointestinal gas may vary greatly according to the type of surgery[5]. In clinical practice, the latter is expected to occur between less than 24 h postoperatively for minor operations such as an appendicectomy and 5–6 days in case of a perforated appendix with peritonitis. The duration of postoperative atony as a criterion for inclusion in this study was fixed at 2 or 3 days. Hence, after extraperitoneal operations, described in *Table 1*, as well as after intraperitoneal operations not resulting in construction of a gastrointestinal anastomosis/ostomy and not being an intervention for peritonitis, bowel function might have recovered already at the start of the trial, or would be at a turning point, and flatus passed spontaneously. Intergroup differences in numbers of patients having passed flatus by a certain time after operation were analysed by means of the Fisher exact probability test (2-tailed probability).

Results

The four study groups were comparable with regard to sex, age and weight of the patients, type of surgery (extra *versus* intraperitoneal, specific operations belonging to these types) and use of pre-, peri- and postoperative medications. The time between the first injection and the end of the operation was also similar in the four groups (*Table 1*). None of the patients had impaired consciousness or was severely ill to such an extent that reporting of the first occurrence of flatus was likely to be unreliable.

Figure 1 shows the occurrence of flatus during the 4 h 'able 1 *Patient and operation data*

	0 mg (*n*=35)	2 mg (*n*=30)	4 mg (*n*=28)	8 mg (*n*=25)	Total population (*n*=118)
ex					
Male	15	18	10	14	57
Female	20	12	18	11	61
'ype of operation					
Extraperitoneal					
Skin, skeleton	2	—	—	—	2
Prostatectomy, orchidectomy	1	1	—	2	4
Vaginal hysterectomy	1	—	1	—	2
(Inguinal) hernia	—	3	1	1	5
Intraperitoneal					
(a) With gastrointestinal anastomoses/ostomies or extensive mobilization of peritoneum:					
Stomach (including vagotomy)	6	6	6	3	21
Small and large intestine	9	12	10	8	39
Peritonitis	1	—	1	—	2
(b) Without gastrointestinal anastomoses/ostomies/peritonitis					
Urogenital	2	—	1	—	3
Gynaecological	4	1	—	—	5
Diagnostic laparotomy	—	1	—	—	1
Gallbladder, liver, spleen	9	6	8	11	34
)uration of operation (min)					
Median	105	90	120	90	90
Extremes	30–300	30–240	30–180	30–195	30–300
'ime between first injection and end of operation (days)					
Mean	1·91	1·81	1·67	1·64	1·76
s.e.m.	0·10	0·16	0·10	0·13	0·06

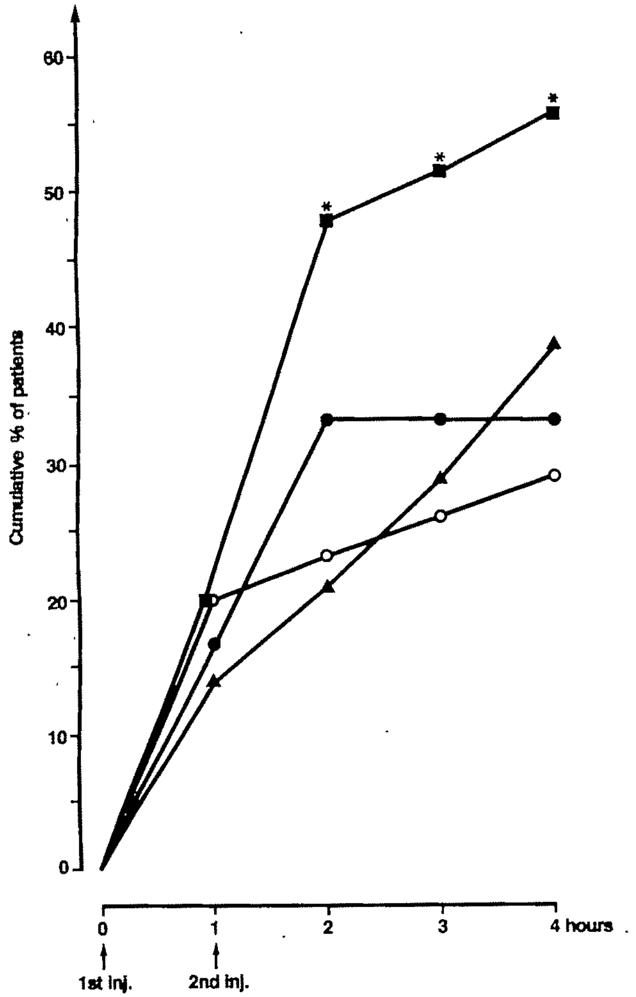

Figure 1 *Occurrence of flatus after any type of operation: effect of one or two injections, each with 0 (○, n=35), 2 (●, n=30), 4 (▲, n=28), 8 (■, n=25) mg of cisapride.* * *P=0·06, cisapride* versus *placebo, Fisher test*

observation period, irrespective of the type of operation. The effect of 2 mg and 4 mg of cisapride on flatus did not seem to surpass substantially the response in the solvent group. Only 8 mg of cisapride were significantly superior ($P=0·06$) to 0 mg 3 h after the second injection.

Table 2 gives, for the different patient groups, the number of patients who passed flatus within 4 h. In the small group of extraperitoneal operations the results were suggestive of a marked spontaneous remission of the ileus. All ten patients, including three of the four in the 0 mg group, who passed flatus, did so within one hour of the first injection. After intraperitoneal surgery, however, the response in the 0 mg group was only 23 per cent. The 2 mg cisapride dose did no better but in the 4 mg group and particularly in the 8 mg group ($P<0·05$) more patients passed flatus.

The results in patients who underwent a gastrointestinal anastomosis or ostomy, or where extensive mobilization of the peritoneum was carried out ($n=2$; 0 mg: no flatus; 4 mg: flatus after 4 h) were compared with those after other intraperitoneal surgery, including uncomplicated elective cholecystectomy, appendicectomy, hysterectomy and explorative laparotomy. Passage of flatus in the solvent group occurred more frequently after the latter type of interventions and was particularly high (33 per cent) in cholecystectomized patients ($n=34$). In the latter patients, the rate of response to 8 mg of cisapride was 55 per cent. Flatus was induced in 50 per cent of the patients given (a double dose of) 8 mg of cisapride in both classes of intraperitoneal operations. The 4 mg dose of cisapride also favourably influenced the appearance of flatus, especially after major operation.

One hour after the first injection, 21 patients had passed flatus: 7/35 (0 mg), 5/30 (2 mg), 4/28 (4 mg) and 5/25 (8 mg). The comparability of the number of patients reaching the study end-point in the four groups, and the fact that these patients passed flatus after having received only half the dose of cisapride, suggest that these patients were near to spontaneous remission of the ileus at the start of the study. The remaining 97 patients, all but three with intraperitoneal surgery, received a second injection. During the next 3 h a low response was noted in the solvent group, especially in those undergoing anastomosis

Table 2 *Effect of injection of single or repeated cisapride on the occurrence of flatus in different patient groups*

	n	Number of patients passing flatus within the 4 h observation period in each dose group			
		0 mg	2 mg	4 mg	8 mg
All patients					
Any operation	118	10/35 (29%)	10/30 (33%)	11/28 (39%)	14/25 (56%)
Extraperitoneal surgery	13	3/4	4/4	0/2	3/3
Intraperitoneal surgery:					
Any	105	7/31 (23%)	6/26 (23%)	11/26 (42%)	11/22 (50%)
Without gastrointestinal anastomoses/ostomies, or intervention for peritonitis	49	4/15 (27%)	2/9 (22%)	4/11 (36%)	7/14 (50%)
With gastrointestinal anastomoses/ostomies, or intervention for peritonitis	56	3/16 (19%)	4/17 (24%)	7/15 (47%)	4/8 (50%)
Patients receiving a repeated dose					
Any operation	97	3/28 (11%)	5/25 (20%)	7/24 (29%)	9/20 (45%)
Intraperitoneal surgery with gastrointestinal anastomoses/ostomies or intervention for peritonitis	53	1/14 (7%)	4/17 (24%)	6/14 (43%)	4/8 (50%)

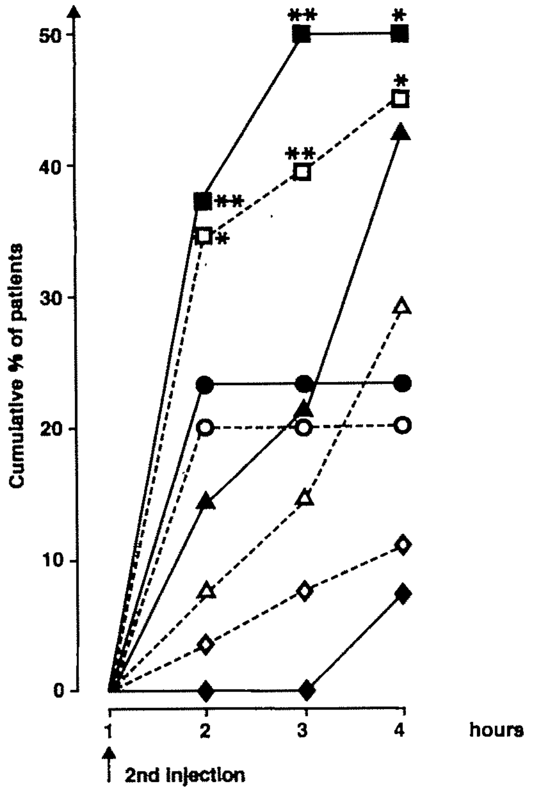

Figure 2 *Occurrence of flatus after a repeated injection of 0, 2, 4 or 8 mg of cisapride: all patients (closed signs) and patients with anastomosis-type of surgery (open signs).* ■, *16 mg* (n=*20*); ▲, *8 mg* (n=*24*); ●, *4 mg* (n=*25*); ◆, *0 mg* (n=*28*); □, *16 mg* (n=*8*); △, *8 mg* (n=*14*); ○, *4 mg* (n=*17*); ◇, *0 mg* (n=*14*). * P<*0·05*; ** P⩽*0·01*, *cisapride* versus *placebo*, *Fisher test*

construction, whereas cisapride had a dose-related effect (*Figure* 2 and *Table* 2). The 2 × 8 mg dose was significantly ($P<0{\cdot}05$) superior to 0 mg as was 2 × 4 mg dose ($P=0{\cdot}08$) by the end of the observation period.

The fact that fixed doses of cisapride were given, irrespective of the patient's body weight, did not devalue the dose–response findings since the weight of responders (i.e. patients passing flatus within 4 h) in each dose group was no lower than that of non-responders, and thus their relative dose (mg/kg) was not higher.

Side-effects were noted in six patients. They were not dose-related and were restricted to symptoms characteristic of an enhanced (i.e. restarted) gastrointestinal motility: abdominal cramps (one in the 0 mg group, two in the 4 mg group), vomiting and/or regurgitation shortly after injection of 2 mg ($n=1$), 4 mg ($n=1$) or 8 mg ($n=1$) of cisapride.

Discussion

It is generally thought that operation itself induces a reflex sympathetic inhibition of gastrointestinal motility, but depression of the cholinergic excitatory system may also contribute to the pathogenesis of postoperative ileus[16,17]. In keeping with the latter possibility, cholinergic stimulation may be used. However, cholinergic agents (e.g. bethanechol and prostigmine) as well as inhibitors of cholinesterase activity (e.g. neostigmine) are not considered the therapy of choice since they induce violent, uncontrollable and incoordinate contractions[10].

Although the present findings require confirmation, they suggest that cisapride may offer an alternative to treatment with cholinergic stimulants. A double dose of 4 mg of cisapride, repeated one hour later, induced flatus in more than 40 per cent of the patients who had undergone an intraperitoneal operation. However, the optimal response was seen after a double dose of 8 mg: already 1 h after the second injection of 8 mg the occurrence of flatus was significantly higher than in control conditions and 2 h later, half of the patients had passed flatus. Thereafter, the patients were no longer followed up. The relative number of cisapride responders was independent of the extent and site of the abdominal operation; this was not the case in the solvent group.

The therapeutic activity of cisapride in postoperative ileus may be explained by improvement of abnormal motor activity, which has been observed at three levels of the gastrointestinal tract. First, cisapride was shown to increase antral and duodenal contractions[18] and to improve evacuation of chyme from the stomach in patients with delayed gastric emptying[19–22]. Second, cisapride corrects impaired small bowel transit of chyme in chronic intestinal pseudo-obstruction[23]. In the cholecystectomized patient, cisapride seems to promote recovery of the small bowel transit[24]. Hyman reported that in a baby with cystic fibrosis—and a lifelong history of feeding problems and constipation—having no postprandial antroduodenal motility, contractions were reintroduced following treatment with cisapride[25]. Third, cisapride improves colon motility, which may be particularly relevant since the colon is considered the major determinant of the ileus[2,5]. Lee and coworkers showed that the colonic transit time in constipated patients was halved after oral dosing with 3 × 20 mg of cisapride[12]. Lederer *et al.* found that cisapride stimulates contractile activity of the distal colon in patients with diabetic enteropathy and constipation[26].

In the assessment of the effect of drugs, bowel sounds and the expulsion of intestinal gas are rather insensitive indicators of gastrointestinal motility and in part rely upon uninhibited, full cooperation of the patient, who has to report to the physician whether or not (s)he has passed gas. Unfortunately, in clinical practice these are often the only tools to which the surgeon can resort. Obviously, objective recording techniques would improve the sensitivity of the trial. However, passage of flatus (only distinct flatus was taken into account) could be indicative of propulsive colonic activity. In fact, neither the recording of pressure from one site of the colon[1,5], nor the return of normal frequency of electrical spike discharge[2] by themselves necessarily correlate with the presence of propulsion or with the time at which gas is expelled from the rectum[5]. Recurrence of propulsion in the small intestine may lag behind segmentation by one to two days[16]. This is unimportant in minor procedures, but atony resulting from intraperitoneal operations, particularly those resulting in construction of gastrointestinal anastomoses/ostomies or involving manipulation of the peritoneum, may last for several days and the associated symptoms may pose a therapeutic problem. Such patients may benefit from treatment with cisapride.

Acknowledgements

The authors thank the hospital nursing staff, Dr L. Akkermans, Dr J. Schuurkes, Dr J. Van Nueten and Dr A. Reyntjens for their critical comments, T. Aerts for his help in the preparation of the manuscript and A. Verbaeten for typing the manuscript.

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Paper accepted 6 February 1987

Br. J. Surg. 1987, Vol. 74, July,
618–619

Accuracy of identification of early gastric cancer

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Two hundred and nineteen patients underwent gastrectomy for cancer in Nottingham University Hospital between January 1978 and December 1985. Twenty of these patients had early gastric cancer (EGC). Barium meal was performed in 15 patients and upper gastrointestinal endoscopy in 15. In all cases, barium meal failed to define the early nature of this disease. Only two lesions were thought to be EGC endoscopically and at laparotomy three were considered to be EGC. As neither radiologist, endoscopist nor surgeon can reliably identify EGC, all patients with gastric cancer in the absence of proven metastases should undergo gastrectomy.

Keywords: Gastric cancer, diagnosis

The overall 5-year survival of patients with gastric cancer is approximately 5 per cent[1]. Early gastric cancer (EGC), defined as tumour limited to the mucosa and submucosa of the stomach on histological assessment, with or without lymph node metastases[2], has a 5-year survival following surgical resection of 70–90 per cent[1,3]. In Europe and the USA 10–13 per cent of patients with gastric cancer undergoing gastrectomy have 'early' lesions[4,5]. However, in Japan approximately 30 per cent of patients with gastric cancer will have EGC[3]. The poor overall prognosis of patients with gastric cancer might lend support to a policy of selective surgery if those patients with early disease who are most likely to benefit from surgery could be reliably identified prior to resection.

The aim of this study was to investigate the ability of clinical investigations to identify patients with EGC. We therefore reviewed radiology, endoscopy and laparotomy findings in all patients in whom a histological diagnosis of EGC was subsequently made.

Patients and methods

We reviewed the pathology reports of all patients in whom a histological diagnosis of gastric adenocarcinoma had been made in Nottingham General and University Hospitals between January 1978 and December 1985. During this period 514 patients with biopsy proven gastric cancer were identified; of these 219 underwent gastrectomy and in this group 20 patients had EGC (9·1 per cent).

The case records and X-rays of those patients with EGC were reviewed, particular attention being paid to patients' symptoms, the results of all pre-operative investigations and laparotomy findings. In 13/15 cases in whom double contrast barium upper gastrointestinal series had been performed, X-ray films were available and were examined by a single consultant radiologist, unaware of the diagnosis or purpose of the study.

Results

EGC was diagnosed in 20 patients (15 men, 5 women) with a median age of 74 years (range 51–87 years). In 7 patients the disease was intramucosal while in 13 there was submucosal involvement. In 10 patients there was associated ulceration. None had histological evidence of lymph node involvement.

Sixteen patients complained of epigastric pain. This was associated with vomiting in 5 and was the presenting complaint in 14 patients. Seven patients had suffered gastrointestinal haemorrhage: six of these presented with symptoms and signs of blood loss, three with symptoms and signs of iron deficiency anaemia and three with acute gastrointestinal haemorrhage.

The median length of symptoms prior to presentation was 6 months (12 h–5 years). The median duration of symptoms in the patients presenting with epigastric pain was 1 year (12 h–2 years).

Table 1 shows the diagnoses made by barium meal, endoscopy and laparotomy in these patients.

In all cases barium meal failed to detect the early nature of the disease, a diagnosis of advanced gastric cancer (AGC) being made in five patients and benign gastric ulcer (BGU) in six. In two patients no abnormality was detected.

Upper gastrointestinal endoscopy was performed in 15 patients. Lesions were identified and biopsied in all but one patient in whom random biopsies were taken. At endoscopy a diagnosis of EGC was made in two patients and confirmed by biopsy; however a further six lesions were mistaken for BGU and three considered to be AGC. In the one patient in whom no endoscopic abnormality was detected, random biopsy revealed a focus of gastric cancer. Initial biopsy findings also altered the endoscopic diagnosis in two patients with BGU and one with gastric polyp, by revealing the presence of

Table 1 *Results of investigations in 20 patients with early gastric cancer*

Provisional diagnosis	Barium meal ($n=15$)	Endoscopy ($n=15$)	Endoscopic biopsy positive ($n=10/15$)*	Laparotomy ($n=20$)
Early gastric cancer	—	2	2/2	3
Advanced gastric cancer	5	3	3/3	7
Benign ulcer	6	6	3/6	6
Gastric polyp	1	3	1/3	1
Other	1	—	—	1
No abnormality detected	2	1	1/1	2

* Numbers of biopsies positive for carcinoma are indicated for each diagnosis made endoscopically

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adenocarcinoma. Three patients underwent repeat endoscopic biopsy (two patients × 2, one patient × 1). This proved one further ulcer to be malignant but misdiagnosed two others as being benign.

A pre-operative diagnosis of gastric cancer was therefore made in 13 patients, however a diagnosis of EGC was only made in 3 patients. The indications for surgery in the remaining patients were gastric polyps in two, symptomatic or recurrent BGU in three, haematemesis in one and suspected leiomyoma in one.

At operation the disease was considered to be advanced in seven patients: in six because of lymph node enlargement and in one because of suspected *linitis plastica.*

Discussion

The majority of patients with gastric cancer have widespread disease at the time of diagnosis; consequently, in a considerable proportion surgery is often palliative. Even when operation is considered by the surgeon to be curative, most patients quickly succumb to their disease. This situation often leads to an attitude of therapeutic nihilism on the part of the clinician which culminates in the pessimistic hypothesis of 'biological predeterminism' expressed by MacDonald and Kotin in 1954, who stated that the outcome of every patient with gastric cancer could not be influenced even by the most determined[6]. There can, however, be little doubt that surgery improves the survival of patients with EGC. While many patients with untreated EGC will survive 5 years without treatment, 70 per cent will by that time have developed AGC, with little chance of prolonged survival[7]. Differentiation of EGC from more advanced forms of the disease is therefore of considerable importance.

In our study the clinical presentation of patients with EGC could not allow their differentiation from patients with advanced disease. Dyspepsia was seen in 80 per cent and though the length of history was long in these patients (median 1 year), in comparison to those who presented with haemorrhage (median 2 months), the range in both was similar (12 h–5 years and 12 h–2 years).

The accuracy of radiological examination was poor despite the use of double contrast techniques. In no patient was a diagnosis of EGC considered either at the time of the original examination or on subsequent review. In its favour, however, radiology did demonstrate a mucosal abnormality in 12/15 patients. Endoscopy enabled visualization of an abnormality in 14/15 patients and, though the lesion seen was considered compatible with a diagnosis of EGC in only two cases, the combined results of endoscopy and biopsy did diagnose malignancy in a further eight patients. Three patients, however, were misdiagnosed as having benign ulcers, despite repeat endoscopy and biopsy in two, emphasizing the need for a high index of suspicion in the investigation of all gastric mucosal lesions and a low threshold for surgical intervention in patients with lesions that do not readily respond to medical management. Pre-operative investigations, therefore, identified a gastric abnormality in 19/20 patients and this finding is comparable to recently reported results from Japan. However, our inability to diagnose EGC pre-operatively is at considerable variance to the Japanese experience[8].

The surgeon, at the time of laparotomy, considered the diagnosis of EGC in only three patients, seven patients being thought to have advanced malignant disease and six a benign ulcer. The results of both pre- and peroperative investigations therefore allowed a diagnosis of EGC to be made in only 3/20 patients.

None of our patients underwent planned pre-operative staging of the extent of their disease. Computerized axial tomography will undoubtedly improve the detection of distant metastases, but it is unlikely to offer any significant improvement in staging all but considerably advanced local disease, as differentiation of inflammatory tissue (including lymph nodes) from malignancy cannot be achieved with sufficient certainty. In this respect, even if nodal involvement could be accurately predicted, it must be remembered that up to 85 per cent of patients with EGC and involved primary lymph nodes (n1) can be expected to live 5 years[9]. Endoluminal ultrasonography may be useful in determining the depth of invasion of gastric cancer, although at present this awaits confirmation and here again differentiation of inflamed from malignant tissue may also prove difficult.

The inability of radiologist, endoscopist and surgeon alike to reliably diagnose EGC either before or at the time of operation, taken in conjunction with a knowledge of the excellent prognosis of EGC following resection, leads us to believe that all patients with gastric cancer in the absence of proven metastatic disease should be considered for surgical resection.

Acknowledgements

We would like to thank the Nottingham surgeons for permission to study patients under their care and Dr P. D. James for reviewing the histology.

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Paper accepted 20 February 1987

Br. J. Surg. 1987, Vol. 74, July, 620–623

Ultrasound-guided percutaneous drainage of intra-abdominal abscesses

The encouraging results of percutaneous abscess drainage (PAD) in simple intra-abdominal abscesses have led us to employ this method in patients with more complex abdominal inflammatory disease, such as those with multiple enteric communicating or multilocular abscesses and patients in whom the percutaneous approach requires puncture routes traversing uninvolved organs. Cure was achieved in 74 per cent of all patients (83 of 112 patients) who underwent PAD, but in only 50 per cent of patients with multiple intra-abdominal abscesses (n = *16), 50 per cent of patients with complex pancreatic inflammatory disease* (n = *8) and 57 per cent of patients with complex intraparenchymal abscesses* (n = *7). PAD contributed to cure in eight of nine patients with enteric communicating abscesses. The transhepatic route to perihepatic abscesses proved to be safe. Complications occurred in nine patients (8 per cent). No relationship was noted between the severity or number of complications and the indication for PAD. Of the 29 failures of PAD, 17 patients were cured by either surgical intervention (14 patients) or a second PAD (1 patient) or a combination of the two methods (2 patients). Twelve patients (11 per cent) died, eight from sepsis due to inadequate drainage. Frequent reassessment by ultrasonography and computerized tomography (CT) in patients with prolonged sepsis after PAD is mandatory. These results justify a place for PAD in the management of the often critically ill patient with complex abdominal inflammatory disease.*

Keywords: Abscess, percutaneous drainage, ultrasound

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The detailed anatomical localization of intra-abdominal abscesses provided by ultrasonography or computerized tomography (CT) has become indispensable for treatment planning. Safe puncture routes are identified by these techniques and in the majority of cases percutaneous abscess drainage (PAD) will be the method of choice[1,2,3]. A comprehensive surgical review referred to this drainage method as 'one of the great advances in abdominal surgery in the past few years'[4]. The good results of PAD in simple unilocular abscesses led to a gradual expansion of the indications for PAD[5,6,7]. Multiple abscesses, ill-defined poorly organized abscesses, interloop abscesses and abscesses in which drainage means traversing uninvolved organs are now also treated by PAD.

In this communication the results of PAD in 112 patients with intra-abdominal abscesses are reported. Special attention is paid to the implications of the new indications for PAD.

Methods

From the 1 January 1982 to the 31 December 1985, PAD was used to treat 139 abscesses in 112 patients at the University Hospital Rotterdam Dijkzigt. All 139 abscesses were confirmed by demonstration of viable bacteria on Gram stain and bacteriological culture. In 34 patients abscesses were caused by organ disease and in 78 patients postoperative abscesses were present. The anatomical sites of the abscesses are summarized in *Table 1*.

A well-defined, unilocular, infected fluid collection, the drainage route to which did not traverse uninvolved organs, was considered to be a simple abscess. All others were called complex abscesses.

Multiple abscesses were present in 16 of 53 patients with intraperitoneal abscesses. Of 29 patients with retroperitoneal abscesses, 8 were considered to have complex, ill-defined abscess formation due to pancreatic inflammatory disease.

Five patients with multiple liver abscesses (four patients with 2–4 synchronous and one patient with 5 metachronous abscesses) and two patients with a splenic abscess were considered to have complex intraparenchymal inflammatory disease. Enteric communicating abscesses were shown on a sinogram in nine patients: four patients had a colonic fistula, four patients a small bowel fistula and another patient a leaking gastrojejunostomy. In all cases of liver, splenic and renal abscesses, puncture routes had to traverse normal parenchyma.

A transhepatic route was chosen in 10 patients with a subhepatic fluid collection, in 3 patients with a right subphrenic abscess and in 1 patient with a right pararenal abscess.

In 94 patients the percutaneous drainage procedure was performed in the radiological department, and in 18 patients in the intensive care unit as a bedside procedure. The majority of the abscesses were diagnosed by ultrasound examination. In doubtful cases or in cases of strong clinical suspicion and a negative ultrasound examination, CT

Table 1 *Anatomical sites of 139 abscesses in 112 patients*

	Site	Total number of abscesses
Intraperitoneal (*n* = 53)	Subphrenic	25
	Subhepatic	10
	Paracolic gutter	25
	Pelvic	9
Retroperitoneal (*n* = 29)	Pancreatic lesser sac	9
	Psoas–pararenal	21
Intraparenchymal (*n* = 30)	Hepatic	33
	Splenic	2
	Renal	5
Total (*n* = 112)		139

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Table 2 *Cure rate following PAD and overall mortality rate in patients with simple and complex intra-abdominal abscesses arranged according to the anatomical sites of the abscess*

	Simple abscesses		Complex abscesses		All patients	
	Cure	Mortality	Cure	Mortality	Cure	Mortality
Intraperitoneal	81%	3%	50%	37%	71%	13%
n	37		16		53	
Retroperitoneal	85%	9%	50%	13%	75%	10%
n	21		8		29	
Intraparenchymal	91%	0%	57%	28%	83%	6%
n	23		7		30	

Table 3 *Diagnosis and sites of abscesses in unsuccessful abscess treatment*

Patients						
Sex	Age	Diagnosis	Site of abscess	P/S	Treatment	Cause of death
M	73 years	Diverticulitis	Intraperitoneal/multiple	P	PAD	Lung embolism
M	74 years	Pancreatitis	Pancreatic phlegmon	S	PAD	Sepsis
M	26 years	Necrotic bowel (vasculitis)	Intraperitoneal/multiple	S	PAD	Sepsis
F	63 years	Recurrence of pancreatic malignancy	Intraperitoneal liver abscesses/multiple	S	PAD	End-stage malignancy
M	48 years	Abdominal trauma	Intraperitoneal/multiple	P	PAD	Sepsis
M	65 years	Infected aortic graft	Retroperitoneal	S	PAD Surgery (L)	Sepsis
M	43 years	Pancreatic malignancy	Liver abscess/multiple	S	PAD Surgery (DA)	End-stage malignancy
M	67 years	Infected aortic graft	Retroperitoneal	P	PAD Surgery (L)	Sepsis
M	62 years	Sclerosing cholangitis	Right subphrenic	P	PAD Surgery (DA)	Variceal bleeding
F	74 years	Diverticulitis	Intraperitoneal/multiple	P	PAD Surgery (L)	Sepsis
F	76 years	Turbo-ovarian abscess	Intraperitoneal/multiple	P	PAD Surgery (L)	Sepsis
M	78 years	Cholecystitis, cholangitis	Intraperitoneal/multiple	P	PAD Surgery (L)	Sepsis

M, male; F, female; L, laparotomy; DA, direct surgical approach to the abscess; P, postoperative; S, spontaneous

was performed. Although all punctures were done under ultrasound guidance, CT played an important role in determining a safe puncture route in complex cases. A diagnostic needle aspiration preceded PAD in every case.

During the first year of this study the catheters used were mainly pigtail catheters (8–10 Fr.), whereas in the last 2 years double lumen sump catheters (12–16 Fr.) were used. When patients were cured without further surgical intervention, PAD was considered successful. Failure of PAD was defined as hospital mortality, recurrence of the abscess or any surgical intervention.

Results

Of 112 patients with 139 abscesses, 83 patients (74 per cent) with 101 abscesses were cured by PAD without surgical intervention. The total number of patients cured either by PAD or by surgical intervention was 100 (89 per cent).

PAD was successful in 50 per cent of patients with multiple intraperitoneal abscesses ($n=16$) as opposed to 81 per cent of patients with a single intraperitoneal abscess ($n=37$). In six cases in which laparotomy was performed unsuspected abscesses were found, the localization often being intermesenteric (*Table 2*).

Patients with retroperitoneal abscesses could be cured by PAD in 50 per cent of cases when pancreatic disease was the cause ($n=8$), whereas, if this cause was excluded ($n=21$), 85 per cent were cured.

In complex intraparenchymal abscesses ($n=7$) PAD was successful in 57 per cent of patients as opposed to 91 per cent of patients with simple intraparenchymal abscesses ($n=23$) *Table 2*).

Of nine patients with enteric communicating abscesses, six required surgical correction of the cause of the abscess with proximal diversion. In one patient both a surgical approach to the abscess and a proximal diversion were necessary. Two patients with a low output small bowel fistula recovered without surgery after long-term drainage (6 and 8 weeks).

Twelve patients died in hospital (11 per cent) (*Table 3*), eight of them with sepsis. Two patients with multiple liver abscesses died of end-stage malignancy. The other two patients died of pulmonary embolism and oesophageal variceal bleeding respectively. Abscesses recurred in five patients (4·5 per cent).

Improper catheter position was shown on a CT examination in a patient with a large pancreatic phlegmon and the position was corrected.

PAD failed in 29 patients. Multiloculation and the presence of necrotic tissue, thick, non-fluid debris or the failure to demonstrate an abscess by ultrasonography or CT were the most common causes. There were five critically ill patients (one with end-stage malignancy), for whom PAD, as a less invasive treatment than surgical drainage, was the only possible approach. Failure in these cases was not followed by any other treatment. In 13 patients surgical drainage was performed after failure of PAD. A second attempt at PAD was made five times: one was successful and four needed surgery. Surgical drainage failed 10 times: six patients died and four were cured by a second surgical drainage. A direct surgical approach to the abscess was performed in ten patients of whom one died. Exploratory laparotomy was carried out in seven patients of whom five died.

Complications

Puncture-related complications were noted in nine patients (8 per cent). In one patient who underwent a Whipple's procedure 6 months previously, a distended efferent jejunal loop was mistaken for a fluid collection. The drainage procedure did not lead to complications and laparotomy showed multiple peritoneal metastases, which were the cause of the blockage of the jejunal loop. Transpleural puncture was complicated by a small pneumothorax in one patient. In another patient pleural empyema followed 11 days after otherwise uneventful catheter insertion into a simple right subphrenic abscess. A small subcapsular haematoma was noted after successful drainage of a renal abscess.

One patient experienced severe septicaemia directly after catheter insertion. Four patients developed chills without hypotension; bacteraemia was confirmed by blood culture.

Delayed complications were noticed in two patients: in one a subcutaneous abscess required incision and drainage 1 week after removal of the catheter and a severe catheter back bleeding occurred 7 days after drainage in a patient with an infected pancreatic phlegmon.

Discussion

It has been claimed that the advantages of percutaneous drainage of intra-abdominal abscesses over surgical drainage are a lower recurrence rate and lower complication rate, lower mortality, lower cost and the possibility of using local instead of general anaesthesia[1,2,8,9]. Furthermore, PAD can be performed as a bedside procedure. Several studies have shown mortality rates of 26–31 per cent for patients undergoing surgical abscess drainage[10,11]. Because the majority of these studies were done before the advent of new diagnostic methods, these results are outdated and therefore not comparable with results obtained by PAD.

Accurate localization of intra-abdominal abscesses is crucial in planning treatment. The morbidity from a missed or recurrent abscess is high. PAD is the logical extension of better diagnostic methods. These methods also led to a new interest of the surgeon in the direct approach to the abscess as introduced by Ochsner and Debakey in 1938[11]. A recent study in which this direct approach was compared with complete exploratory laparotomy showed that laparotomy contributed diagnostically in only 9 per cent of cases[12]. The majority of the unsuspected abscesses were intermesenteric as was the case in our study. The cure rate (80 per cent *versus* 61 per cent), mortality rate (12 per cent *versus* 19 per cent) and recurrence rate (8 per cent *versus* 19 per cent) were all in favour of the direct approach[12] and were more or less the same as the overall results of PAD in our study (cure rate 74 per cent; mortality rate 11 per cent and recurrence rate 4·5 per cent). In a retrospective case-controlled study, in which morbidity and mortality of 27 percutaneously drained abscesses were compared with 27 surgically drained abscesses, the authors found no significant differences[3]. It should be stressed that our own series includes patients who were not suitable for any form of surgical treatment.

With the expanded inclusion criteria for PAD, such as multilocular and multiple abscesses, the ill-defined pancreatic phlegmon, enteric communicating abscesses and splenic abscesses, the overall success rate becomes lower (74 per cent as opposed to 85–90 per cent) and recurrence and mortality rate become higher than in earlier reports[2,6,8]. Only 50 per cent of the patients with multiple intraperitoneal abscesses were cured by PAD whereas 81 per cent of the patients with a single intraperitoneal abscess were cured (*Table 2*).

A major cause of a failed attempt at percutaneous drainage in patients with multiple intraperitoneal abscesses was the presence of an unsuspected and often intermesenteric abscess. In general the prognosis of these patients is very poor: six of eight patients died after failure of PAD, three after subsequent surgical drainage.

Many authors report their success rates as a percentage of cured abscesses[5,6]. In cases of multiple abscesses this can lead to discrepancies between cured abscesses and cured patients. A more realistic approach is to define success rate only as the percentage of cured patients.

The results of PAD in retroperitoneal abscesses depend very much on the aetiology of the abscess[5,6,13]. The overall cure rate was 75 per cent in these cases but only 50 per cent in the cases with pancreatic inflammatory disease (*Table 2*). Catheter drainage is usually not effective for the solid debris of an infected pancreatic phlegmon; these patients require operative debridement, for which the CT image is often an accurate predictor. The clinical condition of these critically ill patients is usually an indication for PAD, as even temporary drainage may be of benefit[13].

Furthermore, the presence of a well-positioned catheter can facilitate the surgical procedure because it indicates the route to the abscess. Several studies report success rates of up to 89 per cent for PAD in intraparenchymal abscesses[5,14]. In our study 25 of 30 (83 per cent) patients with these abscesses were cured without surgery; 3 of them had multiple abscesses. Surgical treatment for a splenic abscess is usually splenectomy, but the benefits of retaining the spleen now justify an attempt to perform PAD[15]. PAD of two haematogenous splenic abscesses caused no complications and although in one patient operative debridement was necessary both patients retained their spleen. Three renal abscesses and two infected renal cysts were treated successfully by PAD.

Surgical treatment of intra-abdominal infection is based on evacuation of pus and control of the source of contamination. In spite of all sophisticated imaging techniques the cause of the abscess formation, especially in enteric communicating abscesses, will only become clear after several days of drainage. Attempts at correcting the leak in the presence of infection are usually unsuccessful and in many cases preliminary PAD brings the patient into a better clinical condition to undergo surgical treatment directed to the cause of the abscess (six of seven patients in our series).

Complication rates for PAD vary in the literature from 4 to 15 per cent[1,2,6,8]. The complications are usually minor and easy to deal with. Accidental puncture of uninvolved organs can be prevented by careful determination of the puncture route, by means of both ultrasound and CT examinations.

In one patient with a Whipple's procedure a distended efferent jejunal loop was not recognized as such and was inadvertently punctured. In our study complications occurred in 8 per cent of patients. There was no relation between the number of complications or their seriousness and the indication for PAD.

A transhepatic route to the subhepatic and subphrenic spaces proved to be safe and is favoured in cases in which there otherwise would be a chance of damaging bowel loops or contaminating the pleural space. Transpleural drainage should be avoided.

The results of PAD in simple unilocular abscesses are better than those of PAD in complex abscesses. However, the low complication rate and the fact that even 'failed' PAD can temporarily benefit the patient justify a place for PAD in the management of the patient with complex inflammatory abdominal disease. Careful monitoring of the patient after PAD includes further diagnostic examinations whenever his clinical condition does not improve. In these patients ultrasound and CT examinations play an important role 1 or 2 days after the initial drainage of multiple or multilocular abscesses. In the event of insufficient drainage, placement of a second or a larger catheter or surgical drainage by a direct surgical approach should be considered. When diagnostic studies fail to delineate an abscess and when the clinical suspicion is high, exploratory laparotomy is indicated. With this strategy a high percentage (89 per cent in our study) of patients with intra-abdominal abscesses can now be cured.

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Paper accepted 4 March 1987

Announcement

Reviews

The Editorial Board of *The British Journal of Surgery* continues to invite review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium of £100. Potential authors seeking advice on the suitability of review topics are advised to contact: Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Glasgow G31 2EU, UK.

Leading articles

The Editors invite submissions of signed leading articles to *The British Journal of Surgery*. These articles should be 600–1000 words in length, should address controversial topics of current interest and should be supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium of £100 is payable on publication. Potential authors seeking advice on the suitability of topics are advised to contact: Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Glasgow G31 2EF, UK.

Surgical workshops

The Editors invite the submission of articles describing technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they can be accompanied by no more than two figures but should not carry supporting references. Articles submitted to the Surgical Workshop series may be subjected to external review and assessment by the Editorial Board before acceptance.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is likely to be high. Authors are advised to restrict such reports to a maximum of 500 words, to use no more than five references and to submit no more than one illustration.

Br. J. Surg. 1987, Vol. 74, July,
624–625

Prospective randomized controlled trial of urethral versus suprapubic catheterization

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Sixty-six patients requiring catheterization in the course of general surgical operations were randomly allocated into two groups. Of the 34 patients catheterized urethrally 16 developed urinary tract infections whereas of the 32 suprapubically catheterized patients only 2 developed an infection ($P<0{\cdot}001$). *Five patients required recatheterization after removal of their urethral catheters. There were no major complications associated with the use of suprapubic catheters. We propose that, when catheterization is required during a general surgical procedure, the suprapubic route is to be preferred.*

Keywords: Suprapubic catheterization

Previous studies have shown that, even with modern methods of catheter-care, between 10 and 50 per cent of patients undergoing bladder catheterization will develop a urinary tract infection[1–3]. Such infections not only prolong hospital stay and are expensive to treat[4], but also cause unpleasant symptoms and may even threaten life[5].

Although it has been thought that bacteria might be introduced into the bladder at the time of catheterization or ascend via the catheter lumen, there is now evidence that extraluminal migration of distal urethral organisms is the most important mode of catheter-induced infection[6,7]. In theory, therefore, this infection rate should be reduced by suprapubic rather than urethral catheterization. In patients undergoing gynaecological operations and in general surgical patients with postoperative retention there is some evidence that this is the case[8]. We have therefore performed a prospective controlled randomized trial to compare the use of suprapubic with urethral catheters in patients requiring a period of bladder drainage following general surgical procedures.

Patients and methods

During the 6 months from January to June 1986 all patients undergoing general surgical operations who were thought to require catheterization were randomly allocated to one of two groups. We catheterize patients when there is a need to monitor postoperative urine output or after an extensive pelvic dissection with or without an anastamosis. One group of patients was urethrally catheterized using a 14F Foley catheter inserted by the surgeon immediately before operation. In the other group, an identical catheter was placed in the bladder peroperatively and was brought through the abdominal wall by an extraperitoneal route. Any patient with a history of urological disease was excluded from the trial.

All catheters were maintained on a closed-drainage system. Urine specimens were obtained immediately following catheterization and daily thereafter for as long as the catheter remained in position. These specimens were obtained by needle aspiration from the catheter drainage tube after it had been clamped for 15 min. A further mid-stream specimen was obtained two days after removal of the catheter.

Urine was examined by inverted microscopy and 0·002 ml was cultured on cystine lactose electrolyte deficient agar. The diagnosis of a urinary tract infection was made when culture of a mid-stream specimen collected within 48 hours of removal of the catheter yielded $\geq 10^5$ colony forming units/ml, or culture of a catheter specimen yielded $\geq 10^4$/ml as a smaller growth could be significant in a patient on continuous catheter drainage. Only three patients had catheter specimens which yielded bacterial counts between 10^4 and 10^5/ml (5×10^4, 6×10^4, 8×10^4) and all their subsequent specimens yielded $>10^5$/ml.

As prophylaxis for bowel surgery, patients received a single dose of metronidazole 500 mg and cephradine 1 g intravenously on induction of anaesthesia. These antibiotics were continued for 48 h in patients considered to be at a high risk of developing an infection and for 5 days when sepsis was already present.

Results

Seventy-one patients were entered into the trial but five were excluded because of inadequacies either in the number of specimens obtained or in their processing. Of the remaining 66 patients (33 male, 33 female), 34 were allocated to the urethral and 32 to the suprapubic group. The mean ages of the two groups were similar (62·3 and 63·7 years respectively) as were their past medical and drug histories. The operations performed are shown in *Table 1*, and the median period of catheterization was 5 days for each group.

Of the 34 patients (male 16, female 18) undergoing urethral catheterization, 16 developed a urinary tract infection (14 whilst on catheter drainage and 2 within 48 h of catheter removal). In contrast, of the 32 patients in the suprapubically catheterized group only 2 developed infections, both whilst they remained catheterized ($\chi^2=11{\cdot}87$, $P<0{\cdot}001$). There was no significant difference between urethral and suprapubic catheter infection rates in men (5/16 *versus* 2/17 respectively). However in women 11 of the 18 urethral but none of the 15 suprapubic catheters were associated with infections ($P<0{\cdot}001$). There were 14 infections in the 50 patients undergoing elective operations (12/24 urethral, 2/26 suprapubic) and 4 infections in the emergency cases (4/10 urethral, 0/6 suprapubic). The duration of antibiotic prophylaxis did not affect the infection rate (*Table 2*). Sixteen patients (nine urethral, seven suprapubic) were receiving steroids perioperatively and none of these developed

Table 1 *Operations performed*

	Catheter		
Operation	Urethral	Suprapubic	Total
Colectomy	24	21	45
Proctocolectomy	3	5	8
Other laparotomy	7	6	13
Total	34	32	66

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Table 2 *Effect of duration of antibiotic prophylaxis on urinary infection rates*

Duration	*n*	Infected	(%)
1 day	45	12	26·7
2 days	7	2	28·4
5 days	14	4	28·4

an infection but in fourteen of these patients an antibiotic course of 48 h or 5 days was given. Seventeen of the eighteen infected patients developed symptoms or a pyrexia and one urethrally catheterized man developed a *Pseudomonas* septicaemia. This patient was not immunosuppressed. Five of the sixteen men with urethral catheters were unable to micturate following catheter removal and therefore required to be recatheterized. One of these five patients had infected urine at the time the first catheter was removed and a further two developed an infection while the second catheter was in place. Three patients with suprapubic catheters failed to pass urine, but it was possible simply to unclamp their catheters. One of these patients developed an infection after two unsuccessful clampings by which time the catheter had been in place for 12 days. No patient required urological surgery to enable spontaneous micturition. In three patients there was some urine leakage around the suprapubic catheter and in one case this persisted for 12 h after the catheter was removed.

Discussion

Before the introduction of closed-drainage systems, bacteriuria was the almost inevitable consequence of an indwelling urethral catheter. Even though this infection rate has now been considerably reduced, it is known to rise with increasing duration of catheterization with 50 per cent or more of catheters infected within 10 days of insertion[1,2,8]. Our urethral catheter infection rate of 41·2 per cent within 5 days and 47·1 per cent within 7 days is undoubtedly high, but we believe should be considered to reflect the true scale of the problem on a busy general surgical ward. The adoption of strict criteria for the diagnosis of infection matches the presence of appropriate symptoms or pyrexia in all but one patient, and suggests that our infection rate is not an overestimate.

The use of antibiotics in the catheterized patient is still controversial. Although there is evidence that bacteriuria can be cleared by short antibiotic courses, in at least half of patients so-treated reinfection occurs within a few days of stopping treatment[2,9]. Furthermore, prolonged courses of antibiotics are both expensive and are liable to encourage the emergence of resistant organisms and yeasts[10]. We found no significant difference in infection rates between the patient groups treated with a single dose or a more prolonged course of antibiotics. We noted with interest that no patient taking steroids developed an infection but that 14 of these 16 patients received more than a single antibiotic dose.

In keeping with previous reports[1,2], we found the urethral catheter infection rate was higher in women than in men. Suprapubic catheterization reduced this infection rate in both sexes but the reduction achieved statistical significance only in women. The two suprapubically catheterized men who developed infections only did so after very prolonged catheterization (12 and 29 days).

A particular advantage of suprapubic catheters is the possibility of affording the patient a trial of micturition and simply unclamping the catheter should this fail. This manoeuvre saved five catheterizations in the three patients who underwent unsuccessful clamping. We were also impressed that four patients who had previously been urethrally catheterized volunteered a distinct preference for the suprapubic catheter. The absence of a urethral cather is sometimes a disadvantage when performing an abdominoperineal resection for rectal carcinoma when a guide in the urethra is helpful. However, this may be suitably provided by a urethral bougie or sound which can be removed at the end of the operation. The fact that these patients are particularly likely to experience postoperative micturition problems is a further indication for suprapubic rather than urethral catheterization.

A potential disadvantage of suprapubic catheterization is the additional cost of using fine-gauge proprietary catheters which may be over ten times as expensive as a standard Foley urethral catheter. We have overcome this problem by the routine use of a Foley catheter placed in the bladder under direct vision at operation and brought out through the anterior abdominal wall extraperitoneally. The only problem we encountered with this method was leakage around the catheter which occurred in 3/32 patients (9·4 per cent). Although the leakage rates reported using finer-guage proprietary catheters are lower (3–5 per cent) approximately 10 per cent of these catheters become blocked and have to be replaced[11,12]. In none of our patients was leakage more than a minor, transient problem: we therefore feel that the more expensive trocar and catheter sets should be reserved for cases of postoperative urinary retention where their additional cost will be offset by the reduced morbidity.

We conclude that routine use of the suprapubic rather than the urethral catheter significantly reduces the risk of developing a catheter-associated infection. Although this effect is most marked in women, the suprapubic catheter has several advantages which are equally applicable to men. It should therefore be the preferred form of elective catheterization in patients undergoing general surgical operations.

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Paper accepted 14 February 1987

Br. J. Surg. 1987, Vol. 74, July,
626–627

Controlled trial of occlusive dressings in healing chronic venous ulcers

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Fifty-six patients with chronic venous ulcers present for a mean of 2·4 years were randomized to either a new occlusive hydrocolloid dressing (Granuflex, Squibb Surgicare) or a porous non-adherent dressing (N A, Johnson and Johnson). In all patients, dressings were applied beneath a standard graduated compression bandage. There was no difference between the two groups, with complete healing in 21 out of 28 (75 per cent) of occlusive dressing patients and 22 out of 28 (78 per cent) with N A dressings by 12 weeks. Careful graduated compression bandaging achieves healing even in the majority of so-called resistant chronic venous ulcers; there was no additional benefit from applying occlusive dressings which tend to be expensive.

Keywords: Venous ulcer, occlusive dressing, graduated compression

Venous ulcers are common and cause considerable morbidity in the adult population of this country[1]. As healing may be slow or never achieved ulcers create persistent and substantial demands on resources. A wide variety of treatments has been used but it is generally agreed that elevation of the legs and compression bandaging are of central importance. More rapid healing in large ulcers can be achieved, even as an outpatient, by some form of skin grafting[2–4]. This is, however, inappropriate for smaller ulcers which may usually be encouraged to heal within 2–3 months without surgical intervention[5]. Experimentally, occlusive dressings provide better conditions for rapid epithelialization of granulating wounds than exposure to air, and a new hydrocolloid dressing (Granuflex, Squibb Surgicare) performed particularly well[6,7]. In this study we compared Granuflex with a commonly used non-occlusive dressing (N A, Johnson and Johnson) beneath standardized graduated compression bandages. Both N A dressings and Granuflex may be left undisturbed for periods of 7 days or longer, allowing their use on outpatients with the minimum demand on nursing services and little disruption of the growing epithelium. This both simplifies and reduces the cost of venous ulcer management.

Materials and methods

Fifty-six patients referred to a venous ulcer clinic were randomized to receive either the occlusive hydrocolloid dressing (Granuflex) or a non-adherent non-occlusive dressing (N A). All ulcers in consenting patients were consecutively included except those more than 10 cm^2 in area which we have previously shown to be better treated by grafting[4]. A full history and examination were performed with Doppler assessment of arterial pressure at the ankles to confirm that the ulcers were gravitational or venous. Swabs for bacterial culture were regularly taken but antibacterial therapy was used only for spreading cellulitis.

Dressing technique

After washing with saline and removal of all loose slough, the allocated dressing was laid on the ulcer and then covered with an absorbant layer of Velband (Johnson and Johnson) which also served to distribute pressure from the bandages.

Bandage technique

A standard below-knee graduated compression bandage was applied over the dressing in all patients. A layer of crepe bandage was used to compress the Velband, followed by a layer of Elset bandage (Seton Products Limited) and a final layer of Coban cohesive bandage (3M Health Care Limited). The pressure under this bandage was measured at four points between the medial malleolus and the knee using a Medical Stocking Tester (Saltzman Limited, Switzerland) in 16 healthy volunteers and achieved a mean (±s.e.m.) at the medial malleolus of 41·8 ± 1·4 mmHg with a gradual fall to 16·9 ± 1·8 mmHg just below the knee. When measured over a 24 h period the pressure on the ankle rose by 5 mmHg during the day, presumably due to foot swelling, and returned to the initial pressure by the following morning.

Follow-up and measurement of ulcer size

All patients were recommended to walk whenever possible and to elevate their legs when at rest. The ulcers were inspected at weekly intervals unless infection or excessive exudate necessitated more frequent attention. The size of the ulcer was measured by tracing the margin onto cellophane, then transferring the outline to a card of known area to weight ratio. The excised tracing on the card was weighed and the area calculated.

Results

On randomization 28 patients were allocated to each group, which were well-matched for age, sex, duration of ulceration, and previous history of venous disease (*Table 1*). Furthermore, ulcer healing investigation by Doppler, PPG and direct foot vein pressure measurements has shown an equal distribution of superficial and deep venous incompetence between the treatment groups.

The mean size of the ulcers on presentation was 3·4 ± 0·4 cm^2 for Granuflex, and 3·1 ± 0·4 cm^2 for N A. The healing rate was calculated as the percentage of the original area healed each week and was minimal over the first 2 weeks as the ulcer desloughed at 2·9 per cent for Granuflex and 2·1 per cent for N A. Over the next 4 weeks healing was rapid at 11·4 per cent for Granuflex, and 15·6 for N A, but this slowed as the ulcer size

Table 1 *Comparability of treatment groups*

	Granuflex ($n=28$)	N A ($n=28$)
Mean age (years)	69·9	67·5
Age range (years)	34–92	30–90
Time since first ulcer (years)	12·9	13·4
Median duration of present ulcer (months)	22	21
Males	11	12
Females	17	16
Previous DVT	7	7
Previous surgery for varicose veins	11	5

DVT, deep vein thrombosis

decreased in the final 6 weeks to Granuflex 3·7 per cent and N A 2·8 per cent (*Figure 1*). There was no difference in mean area or healing rate between the two groups at any time throughout the study period.

Fifteen in each group (54 per cent) had healed by 6 weeks. By 12 weeks, 21 (75 per cent) of the Granuflex group, and 22 (78 per cent) of the N A group had healed completely (*Figure 2*). Again, there was no important difference between the groups. The dressing type did not significantly influence bacterial contamination which had no effect on healing unless cellulitis developed. Streptococcal cellulitis was seen in seven cases (four with Granuflex and three with NA) of which three (two Granuflex and one NA) failed to heal by 12 weeks.

Discussion

Complete healing was achieved with both types of dressing in more than 75 per cent of venous ulcers suggesting that factors other than the dressings are important in encouraging ulcers to heal. Although most would agree that graduated compression is essential in mobile patients, the ideal pressure and a form of bandaging capable of maintaining it have yet to be determined in clinical studies. Based on a combination of Starling's equation and the known range of venous pressures measured at the ankle in normal, varicose and post-thrombotic legs, an external pressure of 35–40 mmHg at the ankle is theoretically required to prevent capillary transudation in legs with severe venous disease[5]. The graduated compression bandaging used in this study exerted a mean of $41{\cdot}8 \pm 1{\cdot}4$ mmHg at the ankle healed 75 per cent of ulcers within 12 weeks.

The moist environment provided by occlusive dressings has been shown experimentally to promote more rapid epithelialization of granulating wounds[6,7]. Clinically, hydrocolloid dressing was reported to be effective at encouraging healing of pressure sores in an uncontrolled trial and in a study of 35 chronic venous ulcers produced 43 per cent complete healing in 12 weeks[8,9]. However, results are conflicting with one study comparing Granuflex and zinc oxide paste, showing no advantage for occlusive dressings, while in a similar study the mean ulcer size had reduced by 67 per cent in the Granuflex group compared with 22 per cent in the zinc oxide group[10,11]. As these results are no better than those achieved by both dressing materials in our study, the evidence of clinical advantage from the use of occlusive dressing for venous ulcers must be questioned.

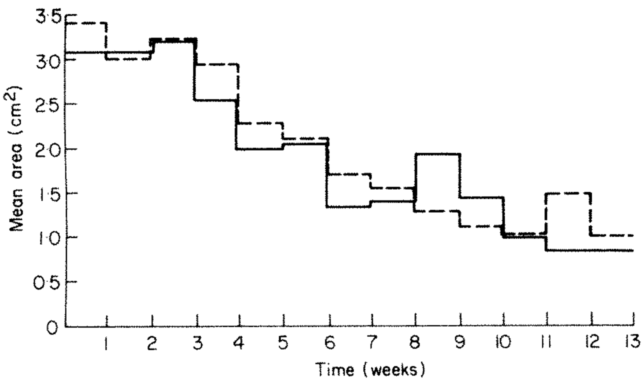

Figure 1 *Mean area of ulcers in the two treatment groups plotted over the 12-week study period; ---- Granuflex, —— N A*

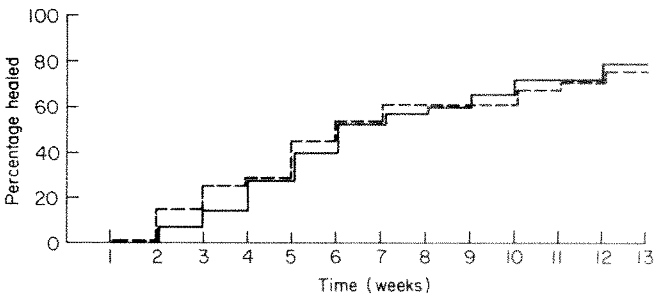

Figure 2 *Percentage of original 56 ulcers healed each week comparing Granuflex (----) and N A (——)*

Granuflex is simple and convenient to use but has a relatively high unit cost, and when applied beneath a four-layer compression bandage produces no faster healing than N A dressings. We have, therefore, failed to show any significant benefit from the use of occlusive dressings in the outpatient management of venous ulcers.

Acknowledgements

We are grateful to the following companies who fund our venous research: Johnson and Johnson Limited, 3M Health Care, Sigvaris (Camp Limited), Zyma UK Limited and Squibb Surgicare, who generously supported this project. Jill Wallace prepared this manuscript to her usual high standard.

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Paper accepted 9 January 1987

Br. J. Surg. 1987, Vol. 74, July,
628–629

Late ischaemic sequelae after umbilical artery catheterization

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The acute complications of umbilical artery catheterization are well recognized but very little is known about long-term consequences. Two cases are presented which indicate that umbilical artery catheterization during the neonatal period may give rise to late ischaemic complications.

Keywords: Umbilical artery catheter, ischaemia, intermittent claudication, renal artery occlusion

Catheterization of the umbilical artery has been used since the early 1960s in critically ill neonates for haemodynamic and blood gas monitoring and subsequently for administration of fluid and drugs. Angiographic studies have shown that catheter thrombosis is common[1–2] but most thrombi are asymptomatic. Symptomatic thrombo-embolic complications of umbilical artery catheterization are rare, but have a poor prognosis[3–6].

This paper presents two patients with long-term sequelae of thrombotic occlusions complicating umbilical artery catheterization.

Case reports

Case 1

This 11-year-old girl with aortic occlusion was born in 1974 prematurely, probably because of cervical insufficiency. Her weight was 1130 g and she was kept on a respirator for around 4 weeks. To nourish the patient and allow blood sampling, an umbilical artery catheter was introduced. After 25 days with the arterial catheter her left leg became blue and then very pale. The catheter was removed and the leg returned to normal. Five days later a red, tender swelling appeared in front of the left knee and within a week developed into an abscess. Incision was performed and gentamicin was instituted because of growth of *Pyocyaneus*. In a fortnight the wound healed but she had X-ray signs of osteomyelitis and gonitis. The leg growth was retarded and from 1983 she could not move as fast as other children and had cold feet. On examination her feet were cyanotic without palpable pulsations. There was a slight pulse in the right groin and no pulse in the left. Her ankle pressure was 65 mmHg on the right side and 70 mmHg on the left. Angiography showed aortic occlusion with extensive collateral development (*Figure 1*). Because of her symptoms and as a preparation for surgery to correct her leg length she underwent arterial reconstruction. A Dacron bifurcation graft (12 × 6 mm) was inserted end-to-side from the distal aorta to the right external iliac artery and the left common femoral artery. She immediately developed warm feet and bilateral pulsation in the posterial tibial and dorsal pedal arteries. At follow-up after 6 months she was well with unlimited walking distance and bilateral ankle–brachial pressure indices of 1·0.

Case 2

When this patient was 2 years old malignant hypertension was detected (BP 280/180 mmHg). As a newborn the patient had an umbilical artery catheter inserted for 9 days because of prematurity and infant respiratory distress syndrome (IRDS). The birth weight was 1520 g after Caesarean section because of maternal eclampsia. On the first day of catheterization there was reversible bluish discoloration of his right leg. On the fifth day it was not possible to aspirate blood from the catheter. The patient was well until hypertension was revealed, but he had had periods of nausea, anorexia and difficulty in walking. Left-sided renin production was 1·5 times that on the right side. Angiography (*Figure 2*) showed post-thrombotic changes in the right iliac artery and an occluded left renal artery with a very small kidney with poor function. A left-sided nephrectomy was performed, the kidney measuring 3 × 2 × 1 cm with a fibrotic reaction around the hilus vessels. Microscopy showed severe nephrosclerosis and no evidence of a congenital renal hypoplasia. The postoperative course was uncomplicated and blood pressure remained normal.

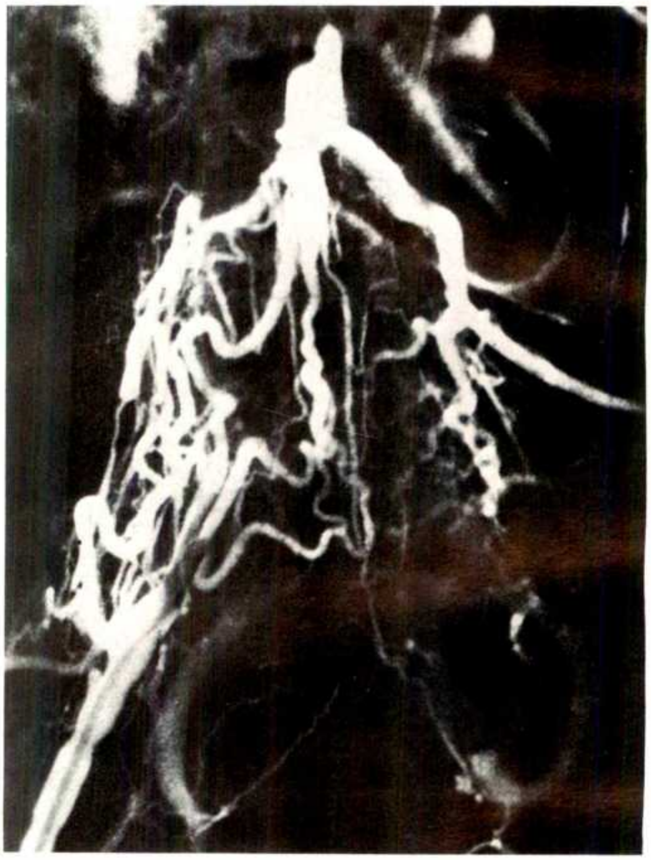

Figure 1 *Patient 1. Transfemoral angiography showing aortic occlusion just above the bifurcation. An abundance of collaterals refills the external iliac artery on the right side and the common femoral artery on the left.*

Discussion

In 1968 Erkan *et al.*[7] reported the first thrombotic complication following umbilical artery catheterization. The frequency of detected aorto-iliac injury after umbilical artery catheterization is very much dependent on the diagnostic method used. Alpert *et al.*[4] found that 5 of 507 catheterized children had limb ischaemia. Neal *et al.*[8] were the first to use pull-out aortography prospectively and found several asymptomatic thrombi, a finding verified by Goetzman *et al.*[2]. The affected children were more commonly female, and had a lower survival rate than babies without thrombosis[2].

Follow-up studies after umbilical artery catheterization are few as blood flow impairment is exceptional[9–11]. The most serious acute complication is aortic occlusion and its reported mortality exceeds 90 per cent[6]. Vasospasm causing cyanosis

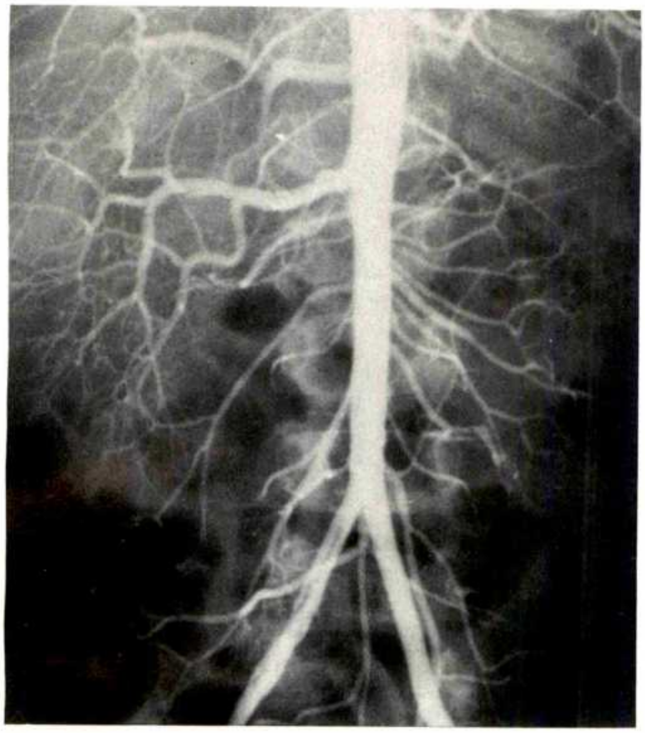

Figure 2 *Patient 2. Aortofemoral angiography showing irregularities in the right common iliac artery and occlusion of the left renal artery*

and blanching of the leg seems to be reversible, causing no sequelae[3,12]. A few cases of renal artery involvement have been described at autopsy[1,13-14], or on scintigraphy[6]. Renovascular hypertension because of renal artery thrombosis after umbilical artery catheterization has been reported[15-16]. One case of irreversible leg paralysis has been ascribed to thrombosis of the thoracic aorta (no angiography) or vasospasm at blood withdrawal[17]. Infective complications are well known[5], and there are reports of mycotic aneurysm detected 12 days to 5 years after catheter use[5,18-24].

As judged from the frequency with which asymptomatic thrombotic complications are detected at autopsy[7-8,25] and aortography[2,10], it cannot be assumed that asymptomatic survivors are free from thrombosis. None the less, long-term occlusive complications are to date extremely rare. Both of our patients had acute ischaemic signs during catheterization but recovered. The knee infection with osteomyelitis in the girl was most probably due to septic embolization, but otherwise she had a very good collateral development which prevented more severe ischaemia. It seems important to follow up children who had umbilical artery catheters more than 10 years ago to establish the frequency of long-term limb ischaemia.

Umbilical artery catheters should be used only when absolutely essential and retained for as short time as possible. To avoid visceral artery thrombosis the catheter is probably best placed in the distal aorta or thoracic aorta with its high flow. The catheter must be removed as soon as there are ischaemic or infective signs or symptoms. Silastic catheters may be less thrombogenic than those made of PVC[26], and Wesström *et al.*[11] found less thrombi in catheters with only one end hole than in those with several side holes.

The treatment of acute aortic occlusion is difficult and the prognosis poor, but with thrombectomy it has been possible to restore the circulation even in very small infants[27]. The two cases reported here illustrate some of the problems encountered in the management of this condition.

Acknowledgement

The study was supported by a grant from the Swedish Medical Research Council (No. 00759).

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Paper accepted 11 February 1987

Br. J. Surg. 1987, Vol. 74, July,
630–633

Duplex scanning of the internal carotid artery: an assessment of cerebral blood flow

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Duplex ultrasound scanning (B-mode imaging and pulsed Doppler shift analysis) was used to measure internal carotid artery blood flow (ICBF) in 20 volunteers. The effect of changes in end tidal CO_2 on cerebral blood flow was measured. When corrected to a P_{CO_2} of 40 torr (5·32 kPa) internal carotid artery blood flow was 286 ± 16 ml min^{-1} (mean ± s.e.m.). Specific CO_2 reactivity (the change in flow per torr change in CO_2) was 8·16 ± 0·69 ml min^{-1} torr^{-1} which was equivalent to 2·0 ± 0·1 per cent of the flow at 40 torr per torr change in CO_2 (percentage CO_2 reactivity). The mean value and the CO_2 reactivity compare favourably with previously reported measurements by other techniques. These data suggest that the non-invasive measurement of internal carotid artery blood flow by Doppler ultrasound scanning is an assessment of cerebral blood flow that can be used to study both normal and pathological changes within the cerebral circulation.

Keywords: Carbon dioxide, internal carotid artery

A variety of techniques has been used to measure cerebral blood flow. These include nitrous oxide wash out[1], xenon-133 (reference 2) and krypton-85 (reference 3) clearance, electromagnetic flowmetry[4] and positron emission tomography[5]. Although the xenon inhalation technique[6] might be termed non-invasive, the currently accepted standard[7] for cerebral blood flow measurement is by intra-arterial injection of xenon[7]. There have been a number of reports of Doppler ultrasound being used to study the cerebral circulation[8–11]. These have not attempted directly to quantify blood flow.

The echo Doppler (Duplex) system of ultrasound scanning (β-mode imaging and pulsed Doppler shift analysis) has been used for many years[12] to image and analyse the pathophysiological changes related to arteriosclerosis of the extracranial part of the carotid system[13]. In this study the Duplex method has been applied to study internal carotid artery blood flow (ICBF) in 20 normal volunteers. The known CO_2 reactivity of the cerebral circulation[14] was used to test whether the Duplex method can be used as a non-invasive means of assessing the cerebral blood flow in health and disease.

Materials and methods

Duplex ultrasound measurement of blood flow

A Diasonics DRF400 Duplex scanner (software version 'H') was used to measure internal carotid artery blood flow. Volume flow is calculated using the following formula[15]:

$$\underset{(\mathrm{ml\ min^{-1}})}{\text{Flow}} = \underset{(\mathrm{cm^{2}})}{\text{Area of vessel}} \times \underset{(\mathrm{cm\ s^{-1}})}{\text{Time average velocity (TAV)}}$$

The area of the vessel is calculated after measurement of its internal diameter obtained from the B-mode image. After uniform insonation of the vessel utilizing the Doppler beam, with a sample volume of between two-thirds and three-quarters of the vessel diameter, the TAV (cm s^{-1}) is calculated from the summation of all the 'instantaneous mean velocities' (50 s^{-1}) for at least five cardiac cycles. This allows for differing velocity profiles. The instantaneous velocity is calculated from the Doppler equation relating frequency of Doppler shift to velocity[15]:

$$V = \frac{V_0 F_d}{2F_0 \cos\theta}$$

where V = velocity of blood flow; V_0 = speed of sound in tissue (1·56 × 105 cm s^{-1}); F_d = Doppler shift frequency; F_0 = transmitted frequency; θ = angle between acoustic axis and flow or Doppler beam and flow.

Resting internal carotid artery blood flow measurement

Internal carotid artery blood flow was measured on the left side in 20 healthy volunteers (mean age 32, 9 males, 11 females). After a 20 min period of rest, measurements were made in the supine position with a 15° head-up tilt. A simultaneous recording of respiratory P_{CO_2} was made with a needle sampler inserted into a closely fitting face mask and analysed by a Beckman LB-2 capnograph. Calibration of the capnograph against room air and 5 per cent CO_2 was maintained throughout the test period.

Systolic and diastolic brachial blood pressures were measured during each of the three room-air breathing periods, during hypocapnia and during hypercapnia. The mean blood pressures were calculated for each period:

$$\text{Mean blood pressure} = \text{Diastolic blood pressure} + \tfrac{1}{3}(\text{systolic} - \text{diastolic})$$

Five simultaneous measurements of internal carotid artery blood flow and end respiratory P_{CO_2} (P_{erCO_2}) were made during an initial period of room-air breathing. Five readings of each parameter were also made following hyperventilation and following 5 per cent CO_2 breathing. The mean resting internal carotid artery blood flow for each subject was calculated from these 15 measurements.

Carbon dioxide reactivity

The effect on internal carotid artery blood flow of varying the end respiratory CO_2 was studied in the same 20 subjects by voluntary hyperventilation and by 5 per cent CO_2 breathing. The assumption was made that with normal pulmonary function, end respiratory P_{CO_2} is equivalent to arterial P_{CO_2}.

From the resting state, subjects were asked to increase their tidal volume and, if necessary, their respiratory rate until a stable state of hypocapnia was achieved. Five measurements of internal carotid artery blood flow and end respiratory CO_2 were made.

After a second resting period during which internal carotid artery blood flow and P_{erCO_2} measurements were made five times to confirm return to baseline values, 5 per cent CO_2 in air was substituted for inspired air until a stable state of hypercapnia was achieved. Five pairs of readings for internal carotid artery blood flow and end respiratory CO_2 were made. Five pairs of resting measurements were made following removal of inspired CO_2 and return of P_{erCO_2} to baseline levels.

Calculation of carbon dioxide reactivity

A linear regression of internal carotid artery blood flow against P_{erCO_2} was computed for each subject (CO_2 reactivity = slope in ml min^{-1} torr^{-1}). The mean resting internal carotid artery blood flow was then corrected to a P_{CO_2} of 40 torr by multiplying the slope by the difference

Table 1 *Comparison of mean resting ICBF with published data*

Flow technique	Author	Mean ICBF (ml min^{-1})	Mean P_{aCO_2} (torr)
N_2O	Kety and Schmidt[17]	261	Not recorded
Xe	Overgaard and Tweed[18]	218·4–273·9	37·5
Electromagnetic flow	Greenfield and Tindall[4] Hardesty *et al.*[19]	201–364	Not recorded
Duplex/Doppler	Leopold *et al.*	254	36·9

ICBF: internal carotid artery blood flow

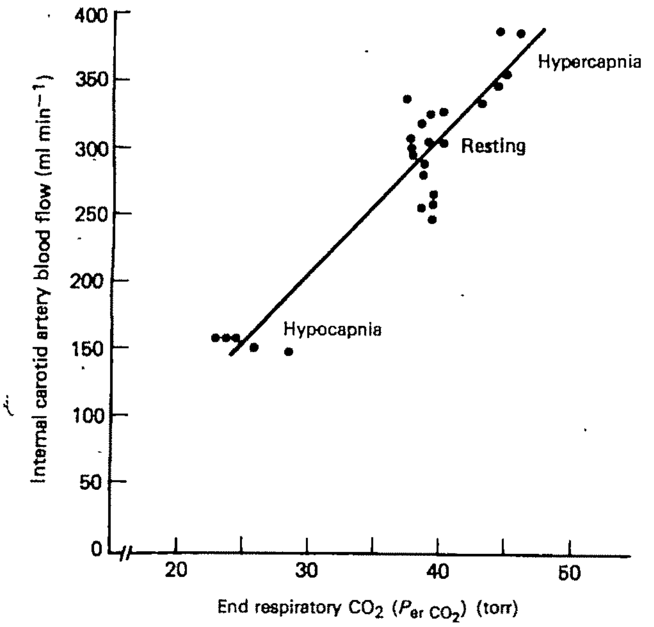

Figure 1 *An individual regression plot for resting, hypocapnia and hypercapnia.* $r=0{\cdot}94$, $P \leqslant 0{\cdot}001$

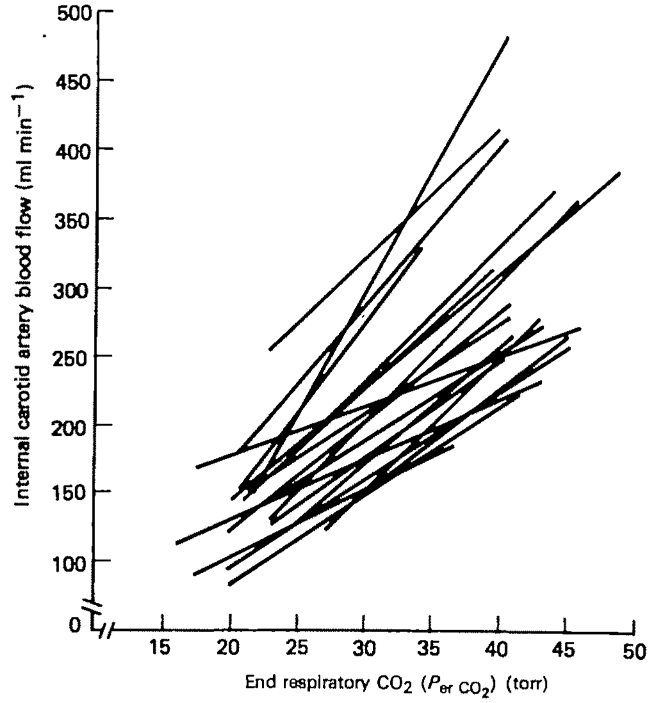

Figure 2 *A regression plot for CO_2 reactivity in 20 normal subjects*

between the mean resting P_{CO_2} and 40 torr and adding that to the mean resting internal carotid artery blood flow. The internal carotid artery blood flow (ICBF) corrected to 40 torr was then used to calculate the percentage CO_2 reactivity.

$$\text{Percentage } CO_2 \text{ reactivity } (\%\,\text{torr}^{-1}) = \frac{100 \times CO_2 \text{ reactivity (ml min}^{-1}\text{ torr}^{-1})}{\text{ICBF at 40 torr } P_{CO_2} \text{ (ml min}^{-1})} \text{ per cent}$$

Cerebral conductance

Conductance was calculated for each determination of blood flow and mean blood pressure. The resting mean cerebrovascular conductance was calculated using the blood flow at 40 torr divided by the blood pressure measured at rest. A linear regression plot of CO_2 reactivity against mean conductance for 13 subjects was constructed in a manner similar to that described by Ackerman[16].

Statistical analysis

All values are reported as mean ± the standard deviation. Linear regression analysis was used to obtain the slope of the relationship between the independent variable P_{erCO_2} and the dependent variable internal carotid artery blood flow. Comparison between internal carotid artery blood flow during room-air breathing, hypocapnia and hypercapnia were done by analysis of variance (Kruskal–Wallis statistic).

Results

Internal carotid artery blood flow

In the normocapnic state the mean resting blood flow was 254 ± 56 ml min^{-1} (mean ± standard deviation) at a P_{CO_2} of $36{\cdot}9 \pm 3{\cdot}7$ torr. Corrected to a P_{CO_2} of 40 torr the mean blood flow was 286 ± 77 ml min^{-1}. *Table 1* compares this with resting normocapnic internal carotid artery blood flow values extrapolated from published data[4,17–19].

Mean blood flow for hypercapnia and hypocapnia was 307 ± 68 ml min^{-1} ($P_{CO_2} = 41{\cdot}9 \pm 3{\cdot}6$ torr) and 155 ± 51 ml min^{-1} ($P_{erCO_2} = 24{\cdot}0 \pm 2{\cdot}8$ torr) respectively. These are significantly different from the resting state ($P < 0{\cdot}01$). Thirteen subjects had a full set of readings, while seven had resting and hypocapnic readings only.

CO_2 reactivity

An individual regression plot for resting hypocapnic and hypercapnic readings is shown in *Figure 1*, and the cumulative plots for the study population are shown in *Figure 2*. Carbon dioxide reactivity and percentage CO_2 reactivity were calculated for each subject and the mean for our study population was computed. The CO_2 reactivity was $8{\cdot}16 \pm 3{\cdot}3$ ml min^{-1} torr^{-1}. The percentage CO_2 reactivity was $2{\cdot}8 \pm 0{\cdot}69$ per cent torr^{-1} which is compared with data obtained by other authors[22–23] (*Table 2*).

Mean cerebrovascular conductance is significantly correlated to CO_2 reactivity in our study population ($r = 0{\cdot}69$, $P < 0{\cdot}01$) (*Figure 3*). Mean blood pressure did not change significantly in any measurement period. It was $88{\cdot}0 \pm 11{\cdot}2$ mmHg in the first room-air breathing period, $89{\cdot}5 \pm 9{\cdot}3$ mmHg during hypocapnia, and $93{\cdot}2 \pm 8{\cdot}0$ mmHg during hypercapnia.

Discussion

Since Doppler ultrasound was first developed to measure blood

Table 2 *Comparison of per cent CO_2 reactivity with published data*

		Per cent reactivity to CO_2		
Source	*n*	Range	Mean	s.d.
Kety and Schmidt (1946)[20]	11	1·19–3·07	1·95	±0·58
Fazekas *et al.* (1961)[21]	9	1·67–8·83	5·12	±2·17
Oleson *et al.* (1971)[22]	14	1·97–3·64	2·86	±0·57
Ackerman *et al.* (1972)[23]	29	0·97–4·83	2·66	±0·90
Leopold *et al.**	22	1·36–4·68	2·80	±0·69

* Data presented in this paper

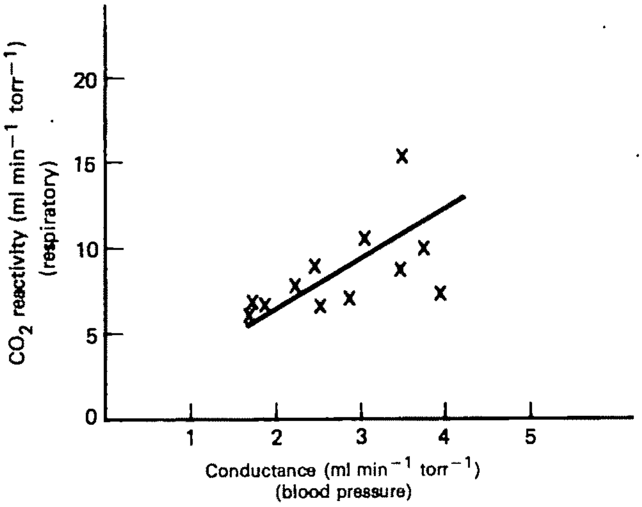

Figure 3 *Correlation between CO_2 reactivity and conductance. $r = 0{\cdot}69$, $P \leqslant 0{\cdot}01$*

velocity within vessels it has been applied to many anatomical sites[24]. These applications include its use as a measure of the degree of flow disturbance caused by arterial stenosis[25] and its ability to construct an image of the artery under study[25] as accomplished by the MAVIS scanner[26]. More recently Doppler ultrasound has been combined with conventional ultrasound imagers allowing the simultaneous imaging and Doppler-shift analysis of blood vessels and the flow within them[12]. Nowhere has interest in the application of this technique been more intense than in the extracranial carotid system. Numerous authors have described changes in Doppler shift analysis relating to the severity of atheromatous disease[25,27,28]. However, little work has been performed using this technique to quantify flow within normal carotid arteries as a reflection of cerebral haemodynamics.

There have been some reports on the use of Doppler ultrasound without imaging to measure flow in the common carotid and anterior cerebral arteries[11,30,31] mainly in relation to the determination of brain death. Changes in peak diastolic and systolic velocity were used as a semi-quantitative measurement of cerebral blood flow. These reports rely on blind means to localize the artery for Doppler analysis. This approach can lead to technical error for two reasons. First, the Doppler beam may not insonate a truly representative sample of the cross-sectional velocity profile causing disproportionate representation of the higher velocity (central stream) or lower velocity (near the vessel wall) elements. Thus uniform insonation is essential for flow to be calculated from the instantaneous mean velocity. Second, turbulent flow leading to flow separation and back eddies occurs in the carotid bulb and, if this part of the carotid system is accidentally scanned, the results may become inaccurate. These two factors can lead to inconsistent Doppler sampling and analysis. In light of the inherent shortcomings of these earlier studies, it seemed a logical progression to apply the technique of Duplex ultrasound scanning to the assessment of blood flow within the internal carotid artery. It allows the internal carotid artery to be visualized and the Doppler beam to be carefully placed at a point of laminar flow, in our experience at least 1–2 cm distal to the carotid bulb[32].

Our results for resting internal carotid artery blood flow correlate well with those of others using nitrous oxide, xenon and electromagnetic flow meters (*Table 1*). Both nitrous oxide and xenon flow figures are expressed by Kety[17] and Overgaard[18] as flow/100 g brain tissue and need to be converted before they can be correlated with internal carotid artery blood flow. We have made the same assumptions as Greenfield[4] for mean brain weight (1400 g) and the proportion of the total cerebral blood flow carried by one carotid artery (one-third). These extrapolated figures for cerebral blood flow encounter two problems when comparison is sought between techniques. First, xenon flow studies will tend to monitor flow within the outer layers of the cerebral cortex where there is a higher concentration of grey matter. Grey matter has a blood flow almost twice that of white matter[14]. Second, nitrous oxide clearance studies utilize venous samples which, even when taken from the jugular bulb, may contain a significant admixture with extracerebral blood[33].

The electromagnetic flow studies performed by Greenfield[4] are perhaps the most closely related to our own in that they directly measure blood flow within the internal carotid artery. However, the mean age of his population appears to be higher than ours which could tend to lower flow values.

Hauge[9] and Bishop[10] have described the use of Doppler ultrasound to evaluate changes in blood flow within the vertebral and common carotid arteries contingent upon alterations in arterial P_{CO_2}. Bishop used 5 per cent CO_2 in air to stimulate increased blood flow through arteriosclerotic internal carotid arteries. He analysed blood flow from changes in the peak systolic velocity. Hauge used graded levels of end respiratory CO_2 to derive a figure for CO_2 reactivity (3·9 per cent torr^{-1}) to provide validity for his Doppler technique. We have similarly determined CO_2 reactivity for a normal population (*Table 2*) and find it correlates well with published data. However, there is significant scatter within these published data, possibly the consequence of the techniques used. The advantage of the present method over that of Hauge is the ability to visualize the internal carotid artery, select a site, and measure its diameter at the point of Doppler sampling.

Autoregulation within the normal cerebral circulation is perhaps one of its most important aspects, maintaining cerebral blood flow in the face of marked changes in systemic arterial blood pressure (60–150 mmHg at normocapnia in normotensive subjects)[14]. There is evidence in brain-injured patients that the autoregulatory capacity of the cerebral circulation is altered[18,34,35]. Blood flow in these patients may be solely dependent upon the pressure changes within the intra- and extracranial vessels. Thus the measurement of internal carotid artery blood flow might be a good indicator of intracranial haemodynamics in the brain-injured patient. Reports in this regard have been numerous and mixed in their conclusions[34–36].

In conclusion, it would appear that the non-invasive technique of Duplex ultrasound scanning may be a suitable method with which to study cerebral haemodynamics through changes in blood flow within the internal carotid artery. Application of this technique to study brain-injured patients provides an easily applied method of assessing the effect that different forms of management may have on cerebral blood flow.

Acknowledgements

This work was supported by NIGMS 15426.

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Papaer accepted 6 February 1987

Br. J. Surg. 1987, Vol. 74, July,
634–636

Acute idiopathic scrotal oedema: incidence, manifestations and aetiology

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Twenty-four children with a total of 31 episodes of acute idiopathic scrotal oedema (AISO) were assessed during a 5 year period. AISO accounted for 30 per cent of all admissions with acute scrotal pathology in this period and was the final diagnosis in 69 per cent of cases in those presenting under the age of 10 years. Although presentation was with unilateral (48 per cent) or bilateral (52 per cent) AISO, considerable overlap between these two groups occurred. Five patients (21 per cent) had recurrent attacks. Fourteen boys (60 per cent) had a history of allergy or had allergic manifestations at presentation compared with an incidence of allergy of 28 per cent in 42 controls ($P < 0{\cdot}05$). AISO is the commonest cause of the 'acute scrotum' in boys under the age of 10 years and is probably allergic in origin.

Keywords: Idiopathic scrotal oedema

Although acute idiopathic scrotal oedema (AISO) is reported as the third commonest cause of acute scrotal pathology in childhood requiring hospital admission[1] very little is understood about the condition. Indeed the paucity of information about AISO in the literature has led some authors to conclude that it is rare[2]. Moreover, the aetiology of AISO remains unknown[3]. Trauma, insect bites, urinary extravasation, infection[4] and allergic processes[5–7] have all been postulated as possible causes, but none has been well substantiated.

After observing a number of other allergic manifestations in children with AISO, the present study was undertaken to examine the incidence and manifestations of AISO and to try to assess the role of allergy in its aetiology.

Methods

All children with the diagnosis of AISO admitted to our unit from the Southampton Health District during the years 1981 to 1985 were included in the study. Care was taken to document the clinical features in each case and to record any allergic manifestations at presentation or in the past history. A control group of 42 children attending the unit for miscellaneous minor surgical procedures was used to ascertain the incidence of allergy in the general population within the same age range. All cases of acute scrotal pathology admitted to the unit in the same 5 year period from the same health district were also noted.

Results

There were 31 episodes of AISO in 24 patients. The average age at presentation was 6·5 years (range 1–18, s.d. ±3·4 years) and 24 episodes (77 per cent) occurred in children under 10 years of age (*Figure 1*). In no case was there a preceding history of trauma or drug ingestion. All patients presented with scrotal discomfort and the bright pink scrotal oedema typical of AISO. Duration of symptoms was 6–48 h. The clinical findings were confined to the scrotum in only 32 per cent of episodes, the remainder having additional involvement of the groin (62 per cent), anterior perineum (42 per cent) or penis (20 per cent). At presentation 15 episodes appeared to have unilateral involvement (6 left, 9 right) and 16 bilateral. However, there was considerable overlap between these two groups as many unilateral cases developed changes extending to the contralateral side, while bilateral cases had one side affected more than the other. Four patients had allergic manifestations present at diagnosis comprising angioneurotic oedema (3) and eosinophilia (1). A further 10 patients had a history of allergic phenomena comprising urticaria (4), asthma (5) and eczema (1). These allergic manifestations occurred in those patients with uni- and bilateral AISO. Five patients had recurrent attacks. Of these patients, three had a single recurrence and two had three episodes each.

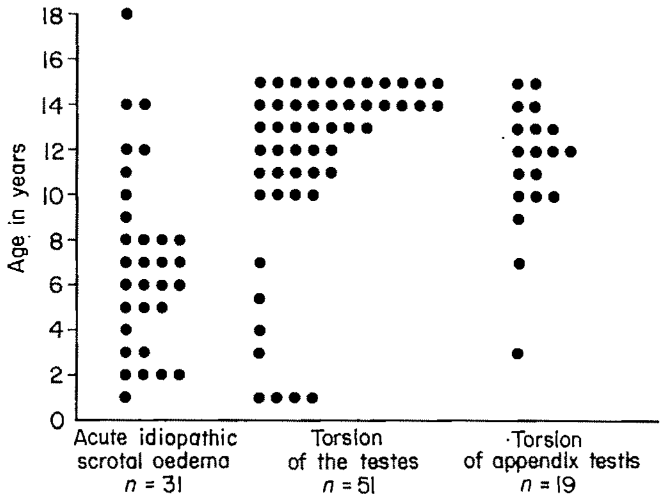

Figure 1 *A comparison of the age of presentation of acute idiopathic scrotal oedema (AISO), torsion of the testes and torsion of the appendix testis in patients who presented between 1981 and 1985*

None of the patients was found to have a primary source of scrotal or perineal infection and no abnormalities were found on external anal examination. A mid-stream urine analysis was normal in all cases.

Seven patients had surgical exploration of the scrotum, one patient having two explorations at two separate presentations with AISO. Operative findings were oedema of the skin and subcutaneous tissues with a normal testis. Swabs taken at exploration in three patients were sterile. Resolution of all episodes occurred within 1–4 days and all patients had normal genitalia at follow-up 2–4 weeks later.

During the study period there were an additional 70 admissions with acute scrotal pathology. Of these, 51 had testicular torsion and 19 torsion of a hydatid of Morgagni. The age distribution of these patients is also shown in *Figure 1*.

Comparison of the 24 patients in this series was made with a control random sample of 42 children (mean age 6·4 years, range

1–18 years, s.d. ±4·9 years). Allergic manifestations either at or before presentation occurred in 14 (60 per cent) of the study group while 12 (28 per cent) of the control group had a history of allergy, comprising reactions to external agents (5), asthma (3), eczema (3) and urticaria (1) ($P<0\cdot05$).

Discussion

AISO is a common but under-reported condition. Qvist[5], who initially described the condition, quoted a 20 per cent incidence in all acute scrotal swellings in childhood and Brereton and Manley[1] noted a 20 per cent incidence in acute scrotal pathology in children. In our series AISO was the second commonest cause of the 'acute scrotum' accounting for 30 per cent of admissions. Furthermore, 77 per cent (24/31) of admissions with AISO occurred in children under the age of 10 years, while only 16 per cent (8/51) of testicular torsions and 16 per cent (3/19) of torsions of the appendix testis occurred in this age group. This notable difference in age distribution makes AISO the commonest cause of the 'acute scrotum' in children under 10 years of age, accounting for 69 per cent of cases.

In the past, distinction has been made between unilateral and bilateral AISO and it has been suggested that the aetiology may be different in these groups[4,5]. The following findings in our series refute this: (i) oedema initially involving one side of the scrotum was often subsequently observed to spread across the midline to affect the entire scrotum; (ii) in cases with bilateral involvement one side was always more affected than the other; (iii) both uni- and bilateral AISO was associated with allergic manifestations elsewhere. We believe, therefore, that uni- and bilateral AISO represent different degrees of spread of the same pathological process.

The most popular theories as to the origin of AISO are those related to allergy[5–7] or infection[4]. Most authors have favoured an allergic cause largely because of the similarity of AISO to angioneurotic oedema, the occasional presence of eosinophilia, the lack of pathogens grown from the oedema fluid and the rapid resolution of the condition without the use of antibiotics. Evidence in favour of an infective origin was produced by Nicholas[4] who found six out of fifteen patients with AISO had a break in the perineal or anal skin and in two of these patients β-haemolytic streptococcus was isolated from scrotal fluid. We have not found evidence of infection in our cases but in contrast have shown a significantly higher incidence of allergic manifestations, either at presentation or in the past, in patients with AISO compared with a control population supporting the theory that AISO is allergic in origin.

Acknowledgements

We would like to thank Mr J. D. Atwell and Mr N. V. Freeman for permission to include their patients in this study.

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Paper accepted 19 January 1987

Br. J. Surg. 1987, Vol. 74, July,
636–638

Orchidopexy: the effect of changing patterns of referral and treatment on outcome

One-hundred and twenty-eight orchidopexies performed between 1979 and 1981 were reviewed in 1985, and the results compared with the results of operations performed in 1972. The age of referral has been determined for 1972, 1979–1981 and 1985. The number of unsatisfactory results has decreased from 35 per cent in 1972 to 9·4 per cent between 1979 and 1981. Five cases of the 'ascending testicle' were discovered, confirming the importance of this phenomenon. We suggest that the optimum age for orchidopexy is during the second year of life; however, during 1985, only 20 per cent of boys referred for orchidopexy were under 3 years of age. Doctors performing neonatal examinations should consider the possibility of cryptorchidism and ensure that affected neonates are reviewed at 1 year. The potential theoretical advantages of orchidopexy at an early age will only be converted into clinical benefit if the operation is performed by an experienced surgeon who has developed an expertise in this area of surgery.

Keywords: Orchidopexy, ascending testicle, cryptorchidism

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In a 1978 report from Leicester, Evans *et al.*[1] documented an 'unsatisfactory result' after orchidopexy in 35 per cent of prepubertal boys who had been operated on 5 years earlier. These disappointing results led us to review in 1985 107 boys who had orchidopexies between 1979 and 1981.

Patients and methods

We reviewed the notes of all those boys who had an orchidopexy between 1979 and 1981 while under the care of a single consultant surgeon with an interest in paediatric surgery. The following data were recorded: age at referral; source of referral; age at operation; side of operation; position of testicle at operation; presence of inguinal hernia at operation; highest grade of surgeon present at operation.

We traced 107 (75 per cent) of those boys who had been operated on and all attended for review. The position and size of the operated testicle was noted. Position was graded as normal, high scrotal, scrotal neck, or superficial inguinal pouch. The last two positions were considered unsatisfactory. Size was recorded as normal or small. Finally, we determined the age and source of referral of boys operated on under the care of the same surgeon in 1985.

Results

Between 1979 and 1981 all orchidopexies were performed using the dartos pouch technique[2], supplemented in 5 per cent of cases by Jones' abdominal extraperitoneal approach[3]. The details of all boys operated on during this period are given in *Table 1*. The operative details of those boys who were reviewed, and the findings on examination at that time are given in *Tables 2* and *3*.

We reviewed 128 orchidopexies and found 10 small testicles, 2 of which were noted to be small at operation. Two testicles of normal size were in a high position at review. Therefore a total of 12 orchidopexies (9·4 per cent) produced an unsatisfactory result. Eight of the ten small testicles were in a satisfactory position. Four boys had undergone re-operation by the time of review and three boys were re-operated on as a result of review. The re-operation rate was 5·5 per cent (cf. 5·6 per cent in 1972[1]). Scrutiny of the details of those boys with an unsatisfactory result after orchidopexy revealed that there was no significant difference compared with the group as a whole, with respect to age at operation, pre-operative position of testicle, grade of operator and bilateral operations.

During the review it became apparent that in five cases the testicle that had been in a normal position at the time of contralateral orchidopexy had since ascended. The observation that the testicle had been correctly situated had been made in all cases by a registrar or consultant. The mean age at subsequent orchidopexy for the ascended testicle was 12·3 years, the change in position of the testicle occurring between the ages of 7·5 and 14 years. One of these five boys had an associated hernial sac at operation.

Discussion

Although it is not feasible to make statistical comparisons between the 1972 and 1979–1981 groups, the similarity of the data concerning side of orchidopexy and incidence of inguinal hernia suggests that the two groups are derived from a similar population of boys. The 9·4 per cent incidence of unsatisfactory results from 1979–1981 group compares favourably with that of 35 per cent in 1972 and with that of other studies (7·2 per cent–65 per cent)[4–9]. The re-operation rate by the time of review at 5 years is similar for the 1972 and 1979–1981 groups, indicating

Table 1 *Details of boys undergoing orchidopexy in 1972, 1979–1981 and 1985*

No. of boys	1972 (141)	1979–1981 (143)	1985 (85)
Mean age at referral	Not available	6·4 years	4·4 years
<3 years old at referral	5·0%	14·0%	38·0%
3–10 years old at referral	64·0%	68·5%	54·0%
>10 years old at referral	31·0%	17·0%	8·0%
Source of referral			
General practitioner	73·0%	60·0%	65·0%
School medical officer	19·0%	23·0%	9·5%
Consultant paediatrician	2·8%	15·0%	24·0%
Consultant surgeon	0·0%	2·0%	1·5%

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Table 2 *Operative details of those patients who were operated on between 1979 and 1981 compared with those operated on in 1972*

No. of boys	1979–1981 143	1972 141
Side of operation		
Right	68 (47·5%)	64 (45·6%)
Left	48 (33·5%)	43 (30·4%)
Bilateral	27 (19·0%)	34 (24·0%)
Inguinal hernia	79 (46·5%)	85 (48·0%)
Position of testicle at operation		
Superficial inguinal pouch	125 (69·7%)	
Inguinal canal	35 (25·0%)	
Intra-abdominal	3 (2·0%)	Not recorded
Ectopic (perineal)	5 (2·0%)	
Absent	2 (1·3%)	
Grade of surgeon		
Consultant	88 (62·0%)	53 (38·0%)
Registrar	51 (35·0%)	84 (60·0%)
SHO	4 (3·0%)	4 (2·0%)

Table 3 *Details of findings at review*

No. of orchidopexies	1979–1981 128	1972 142
Position of testicle at review		
Normal	117 (91·4%)	82 (96·0%)
High scrotum	5 (3·8%)	—
Scrotal neck	2 (1·6%)	—
Superficial inguinal pouch	2 (1·6%)	4 (4·0%)
Size of testicle at review		
Normal	116 (90·0%)	59 (69·0%)
Small	10 (7·8%)	27 (31·0%)
Absent	2 (1·6%)	—

The numbers given from the 1972[1] study are for 86 unilateral orchidopexies. The figures for bilateral orchidopexies are not stated although the percentages of unsatisfactory results are the same after unilateral and bilateral orchidopexies

that the improved results in the latter group had not been achieved by further surgery.

In 1972 four methods of orchidopexy were used. They were the placement technique of Cabot and Nesbit[10], the dartos pouch technique[2], the Ombrédanne[11] procedure and the Torek[12] operation. Between 1979 and 1981 only the dartos pouch method of orchidopexy was used, supplemented in 5 per cent of cases by Jones' approach[3]. Evans[1] found that 31 per cent of testicles operated on in 1972 were atrophic 5 years later. This may be due in part to the fact that the surgical emphasis at that time was on traction rather than mobilization.

Between 1979 and 1981, many more orchidopexies were performed by a consultant surgeon (*Table 2*) than in 1972. The fact that the consultant surgeon had a paediatric interest may have contributed to the improved results that were achieved in the 1979–1981 group. The other important factor to be considered when assessing the results of orchidopexy is age at operation. Between 1979 and 1981 three times as many boys under the age of 3 years were referred for surgery compared with 1972 (*Table 1*). Histological studies[13–16] have shown that the cryptorchid testicle is abnormal from 6 months of age, and that the degree of abnormality increases with time. This histological abnormality is reflected in a small testicle and indeed boys with small testicles after bilateral orchidopexy have greatly reduced fertility compared with those with normal-sized testicles[17]. There is evidence[18] that orchidopexy can improve the histological abnormalities in 70 per cent of testicles, with marked improvement occurring in 22 per cent. Kiesewetter *et al.*[18] were unable to demonstrate that the improvement in histological appearance was greater if orchidopexy was performed at a younger age. However, the histological abnormalities seen in cryptorchid testicles are not so marked in very young boys, making it more difficult to show an 'improvement' after orchidopexy.

Orchidopexy has been reported to carry a significant risk of testicular damage and subsequent atrophy[19], and it might be thought that testicular damage is more likely to occur in very young boys. However, of the ten small testicles that were found at review of the 1979–1981 group, only one boy had been operated on before the age of 3 years. Looked at in more detail, the 14 per cent of boys aged under 3 years who were operated on between 1979 and 1981 contributed to 10 per cent of small testicles at review, while those boys between 3 and 10 years of age contributed to 68·5 per cent of operations and 90 per cent of small testicles at review. These figures suggest that provided the operation is performed by an experienced surgeon, testicular damage is not more likely to occur with younger age at orchidopexy. In summary, we feel that the younger age at operation of the 1979–1981 group may have contributed to its reduced incidence of testicular atrophy.

The optimum age for orchidopexy has yet to be determined. Factors to be considered are subsequent fertility, the risk of testicular malignancy and psychological sequelae. It has been suggested[20] that psychological trauma is minimized if the operation is performed either before 6 months, or between the third and fifth birthday. On the basis of histological studies Mengel *et al.*[16] suggest that orchidopexy should be performed in the first two years of life; however, there are no fertility studies on unilateral cryptorchid boys that show conclusively that operating on very young boys has any effect on subsequent fertility. Staged vasectomy studies[21] do not lend support to early operation. In the case of bilateral cryptorchidism all untreated patients have low sperm counts, 75 per cent being azoospermic. Most studies conclude that approximately 75 per cent of treated patients have low sperm counts. Treatment by orchidopexy before the age of 8 years compared with after the age of 8 years resulted in only very slight benefit in terms of fertility[22].

The relative risk of developing malignancy in an undescended testicle has been a source of contention for many years. Values vary from 118 for an abdominal testicle[23] to 3·7 for all men giving a history of cryptorchidism[24]. The recent case control study by Pottern *et al.*[24] is the first to demonstrate a reduced relative risk of developing testicular cancer with earlier age at orchidopexy, although there are no data for boys operated on aged under 5 years.

During the review we found five boys whose previously descended testicle had ascended. Spontaneous ascent of the testicle was observed in 1966 by Villumsen *et al.*[25] who noted ascent of the testicle in 1·6 per cent of boys examined at 1 and then 3 years of age. Atwell[26] documents ten cases of ascent of the testicle. He postulates that this ascent may be due to alterations in the length of the inguinal canal with growth and to partial absorption of the processus vaginalis into the parietal peritoneum.

Hadziselimovic *et al.*[27] suggest that ascent of the testicle may explain the findings of Mackellar *et al.*[28] that the frequency of orchidopexy in boys aged 2–10 years is more than twice what would have been expected according to the reported incidence of cryptorchidism at 1 year. Further support for the 'ascending testicle' has recently come from Oxford[29], where it was found that 40 per cent of boys whose testicles had not descended at birth but had done so by 3 months became cryptorchid by the age of 1 year. Certainly the ascending testicle invalidates the practice of referring to a boy's infant record to determine whether a testicle at a later date is retractile or truly undescended[30].

Three boys were re-operated on as a result of this review, their testicles having been in a satisfactory position 6 weeks after orchidopexy but were found to be too high at review 5 years later. Evans *et al.*[1] found four high testicles at review, these testicles having been in the scrotum 1 month after orchidopexy. It is not surprising that it should take some time for a testicle to settle into its final postoperative position, and we feel that it would be more sensible to examine children 1 year after orchidopexy in an attempt to detect all those testicles whose final position is unsatisfactory.

If it is accepted that orchidopexy is best performed during the second year of life, then during 1985, only 20 per cent of boys in our series were referred for orchidopexy early enough for this to be achieved. This does represent an improvement on 1972, the reduction in referral age being due to more referrals from paediatricians. Scorer[31] demonstrated that the 2·7 per cent incidence of cryptorchidism in term boys has reduced to 0·7 per cent by 1 year of age. All children in the UK have neonatal examinations. We propose that boys with undescended testicles at birth should be seen by a consultant paediatric surgeon at 1 year of age; by then 75 per cent of undescended testicles will have descended, leaving 25 per cent of the total requiring orchidopexy. Review at 1 year will also ensure that those cryptorchid neonates whose testicles have descended by 3 months only to ascend again by 1 year[29], are not prematurely discharged from follow-up. This policy requires that doctors performing neonatal examinations should be both educated and vigilant concerning the undescended testicle.

The theoretical advantages of performing orchidopexy in the second year of life have not yet been proven. We have found no evidence in Leicester that operating on very small boys increases the incidence of testicular atrophy. However, a long-term prospective study looking initially at testicular size and later at testicular function of boys operated on during the second year of life is urgently needed. Finally, we suggest that junior surgeons performing orchidopexy should be properly trained and supervised, preferably under the auspices of one or two surgeons in each district general hospital. This policy which has been shown to be advantageous in other areas of paediatric surgical practice[32–34] would surely benefit cryptorchid boys.

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Paper accepted 23 March 1987

Br. J. Surg. 1987, Vol. 74, July,
639–642

Model of TPN-associated hepatobiliary dysfunction in the young pig

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Gallbladder 'sludge' and cholestasis are two common complications associated with total parenteral nutrition (TPN), but the aetiology of each is uncertain. An animal model has been developed in the young pig which demonstrates these two complications. Five female piglets, of Landrace Large White Cross variety weighing 4·5–5·9 kg, received nutritional support for 2 weeks with a continuous infusion of TPN solution at a dose of 150 kcal kg^{-1} day^{-1}. The solution was 35 per cent dextrose, 5 per cent L*-amino acids with conventional electrolyte, mineral and vitamin additives. No lipid was used in the solution. Five weight-matched animals were used as controls. All animals in the TPN group developed 'sludge' in their gallbladders, decreased basal bile flow, decreased bile salt excretion and a diminished response to bile salt stimulated bile flow, as compared with controls. There was no abnormality in routine liver function tests or liver histology. It is concluded that TPN therapy in this animal model is associated with the appearance of gallbladder 'sludge', and cholestasis as demonstrated by direct bile flow studies. It is suggested that this bile flow abnormality is due to a decrease in bile salt dependent and bile salt independent fractions of canalicular bile flow. The model provides the opportunity to investigate TPN related hepatobiliary dysfunction in an animal that has similar liver function to man and comparable nutritional requirements.*

Keywords: Swine, parenteral hyperalimentation, cholestasis, cholelithiasis

Abnormalities in liver function tests compatible with cholestasis are common in patients receiving total parenteral nutrition (TPN)[1]. Although such changes were thought to be of little importance, recent reports have indicated that TPN therapy is associated with biliary sludge[2], acalculous cholecystitis[3,4] and gallstones[5] in both children and adults. Cirrhosis may develop in children[6]. Although the biochemical evidence of TPN-related cholestasis reverses when the therapy is stopped[7], subtle abnormalities in liver biopsy material may persist[8–10]. In view of the wide application of parenteral nutritional support in clinical practice, an understanding of the mechanisms of these TPN-related complications is essential.

Clinical studies of TPN-related hepatic dysfunction are difficult because of a variety of factors in the patients which may interfere with hepatic function. These include hepatic functional immaturity[11], fasting[12], malignancy, sepsis[13,14], varied and complex drug regimes[15] and pre-existing organ dysfunction. An animal model is therefore essential to study the specific effects, if any, of TPN.

There are many similarities in liver function between man and the pig[16,17]. Previous studies in our laboratory have demonstrated the suitability of the pig as an animal model to investigate the causes of acute liver dysfunction in patients[18,19]. Moreover, the nutritional requirements of man and the pig are similar[20,21] and thus it should be possible to provide adequate nutritional support in the pig using clinical TPN regimes, an essential requirement in establishing an animal model with clinical relevance. We now report the development of a TPN model in the young pig, and the observation of associated hepatobiliary dysfunction after 2 weeks of treatment.

Methods

Animals

Female piglets (Landrace Large White Cross) of 4·5–5·9 kg body weight were used. Pigs were purchased from a commercial minimal disease piggery and litter mates were randomly distributed into the two experimental groups. Pigs receiving TPN were isolated from the central animal holding area to minimize the potential stress of food smells and the noise of routine animal care. All pigs were housed under identical environmental conditions in 2 × 2 m individual pens and were held in the unit for a minimum of 7 days before the experiment. The control pigs were fed a custom made high protein, low residue diet formulated from NIH recommendations[22] for pigs of this age.

Surgical preparation

Three days before the definitive study, under halothane/oxygen anaesthesia, a polyvinyl central venous catheter (Dural Plastics Pty. Ltd. (i.d. 1·0 mm)) was inserted into each external jugular vein, a large wedge liver biopsy (2–3 g) was taken immediately the abdomen was opened. All procedures were performed under standard antiseptic conditions and no postoperative antibiotics were used.

The TPN solution

Minimal nutritional requirements for pigs of comparable age indicated that a solution equivalent to 150 kcal kg^{-1} day^{-1} with a protein: carbohydrate ratio of 1:7 was necessary. Preliminary studies with a solution of 1 kcal ml^{-1} indicated that a solution of this caloric density could not be delivered at the rate required without producing pulmonary oedema. A solution with a caloric density of 1·4 kcal ml^{-1} did not produce this complication, and therefore was used in the definitive study. When mixed, this TPN solution contained 35 per cent dextrose and 5 per cent synthetic amino acid (Travenol, Australia) with conventional additives (*Table 1*). A single dose of vitamin A (4000 units) and vitamin D (500 units) was given intravenously at the beginning of the infusion. Lipid was not given since it is implicated in causing hepatic steatosis[10], and hence would have been a possible confounding variable in the development of this animal model.

Method of solution administration

Pigs were placed in metabolic cages (2 × 1·5 m) constructed to provide close visual contact between pigs. The intravenous fluids were given using a constant infusion pump (Holter model 908) which was connected to the pig via a high tensile manometer tubing (AHS/Australia: 86–454) with a rotation Luer-lock connector (Cobe

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Table 1 *Electrolyte and vitamin additives to the TPN solution*

Electrolytes	(mmol/l)	Vitamins	(mg day^{-1})
Na	70	Thiamine	250
K	85	Riboflavin	5·5
Mg	45	Pyridoxine	50
Acetate	150	Ascorbic acid	500
Cl	70	Nicotinamide	160
Phosphate	44·5	Vitamin K$_1$	10
Calcium	2·2		
Zn	0·076		

Laboratories, Colorado; 41-280000) to prevent the tube from kinking. The previously placed central venous line was enclosed in the pocket of a material harness and this was connected to the manometer tubing via a three-way tap (Cobe Laboratories, 41-21-001). Tension on the manometer tubing was maintained by means of a simple counter balance. This assembly permitted the pig freedom of movement without kinking or interference with the infusion line.

Experimental design

Pigs were randomly distributed into two groups of five animals. The control group received a constant infusion rate of 4 per cent dextrose 0·2 M saline (Travenol, Australia) at 5 ml h^{-1}. These pigs were permitted food and water *ad libitum*. The study group received TPN solution (150 kcal kg^{-1} day^{-1}); the rate of infusion was adjusted every fourth day to match weight gain. These pigs had access to water only.

Terminal study

After 14 days of fluid administration a terminal study was performed. Under a general anaesthetic (halothane/oxygen) a tracheostomy was performed and an endotracheal tube (Portex, England; size 6·0 mm) was inserted. Ventilation was continued with positive pressure ventilation (Drager, FRG) and anaesthesia was maintained with relaxant and gaseous mixture (Alloferin (0·3 mg kg^{-1}); 1·0 per cent halothane and nitrous oxide:oxygen; 2:1). A wedge liver biopsy was performed, the gallbladder was removed and gallbladder bile collected. A cannula (Tuta, Australia; ref 50.306) was inserted into the common bile duct to permit total bile collection. The portal vein was cannulated (Dwelcath 15 FG; Tuta, Australia) to permit the infusion of taurocholic acid (TCA) and secretin. The external carotid artery was cannulated (Dwelcath 15 FG) and blood pressure was continuously monitored using pressure transducers (Statham) connected to a Grass polygraph. Arterial blood samples were collected at half hourly intervals. Pa$_{O_2}$, Pa$_{CO_2}$, and pH were measured using microelectrode analysis (Radiometer, Copenhagen). Rectal temperature was monitored by a thermistor probe (Yellow Springs Instruments Co.).

Bile was collected in 10 min aliquots, the volume was recorded and it was then stored at −20°C for further analysis. Three basal collections were made and a solution of TCA (Sigma) was then infused via the portal vein. Incremental 10 minute infusion rates of 1·0, 2·0, 5·0, 10·0 and 20·0 μmol min^{-1} kg^{-1} body weight were used. At the completion of the TCA infusion two further collections were taken to demonstrate a return to basal levels. An infusion of secretin (Boots, England) at 2 Crick Harper Raper units min^{-1} was given over 20 min via the portal vein. Two further bile collections were made at the end of this infusion. The pig was then killed with an overdose of barbiturate and an autopsy was performed. Liver weights were recorded and the carcass was eviscerated and stored at −20°C for composition studies. Evisceration was considered necessary to avoid any possible discrepancy due to faecal contents in the enteral-fed pigs.

Measurements

Sequential measurements were made in all animals to assess the adequacy of nutrition and hepatobiliary function.

Nutrition

The adequacy of nutrition was assessed by body weight gain (g day^{-1}) estimated from fourth daily records, serum albumin concentration measured at the beginning and end of the study and terminal nitrogen balance measurements. The whole carcass was analysed for water, protein, fat and ash content[23]. Blood sugar, electrolytes and creatinine were measured.

Hepatobiliary function

Serum bilirubin, alkaline phosphatase (ALP), alanine amino transferase (ALT), γ-glutamyl transpeptidase (GGT) were measured at the beginning and the end of the study using a centrifugal analyser (Roche Diagnostica, Cobas Bio). The livers and gallbladders were assessed macroscopically and microscopically. The histological assessment was made by an independent pathologist without prior knowledge of the study group or sample identification. Biliary secretory function was measured by direct bile flow studies. Bile flow (μl min^{-1} g^{-1} wet liver weight), and bile salt excretion (μg min^{-1} g^{-1} wet liver weight) were calculated following the measurement of bile salt concentration according to the enzymatic method of Talalay[24] as modified by Admirand and Small[25].

Statistical analysis

Differences between groups were tested by Student's *t* test when parametric or the Mann–Whitney *U* test when non-parametric. Relationships between sets of data were established by linear regression analysis for each animal and the significance of differences between groups was tested by Student's *t* test applied to the slopes and intercepts of the regression line for each animal.

Results

There were no complications of the infusion procedures. There was no catheter sepsis as determined by quantitative catheter tip culture[26], nor was there post-mortem evidence of bacterial endocarditis, pulmonary sepsis or pulmonary oedema. The pigs tolerated the infusion procedure and there was no evidence of stress as indicated by the absence of abnormal stereotypic behaviour and gastric ulceration. Except for the sludge in the gallbladder (see below) no other abnormality was found at postmortem examination. One of the control group was eliminated from the series (one of six) due to the development of an intussusception, apparent on the fifth postoperative day.

Nutritional assessment

All animals were in positive nitrogen balance. All pigs gained weight, although the rate of gain was significantly less in the TPN group (126 g day^{-1} ± 54; mean ± s.d.) as compared to the controls (263 g day^{-1} ± 22; mean ± s.d.). The carcass compositions of the two groups were comparable (*Table 2*). There was no significant difference during the study period either between or within groups in the levels of serum proteins, serum electrolytes or blood sugar (*Table 3*).

Hepatobiliary assessment

Light microscopy of liver biopsy specimens showed no evidence of intrahepatic cholestasis or fatty infiltration. However, in all

Table 2 *Relative content of fat, water, ash and protein in the carcass from pigs receiving TPN and from controls*

	Control	TPN
Fat	13·7±1·6	14·4±1·2
Water	68·3±1·2	68·7±1·6
Ash	3·4±0·4	2·9±0·24
Protein	14·5±0·8	14·1±0·76

Values are mean percentages of total carcass composition ± s.d.

Table 3 *Serial values of routine liver function tests, albumin and glucose in serum samples collected at the beginning and at the end of the infusion period*

	Control		TPN	
	Start	Finish	Start	Finish
Bilirubin (μmol l^{-1})	2·8±1·5	2·6±1·5	2·2±1·6	2·5±1·7
ALP (units l^{-1})	177±51	214±79	211±97	181±44
ALT (units l^{-1})	15±4	26±13	17±4	20±10
GGT (units l^{-1})	30±11	33±11	24±10	18±8
Glucose (mmol l^{-1})	5·0±1·0	5·0±1·3	4·7±1·2	5·0±2·3
Albumin (g l^{-1})	21·8±3·0	24·4±2·8	19·6±4·1	20·2±5·9

Values are means ± s.d.
ALP; alkaline phosphatase; ALT, γ-glutamyl transferase; GGT, glutamyl transpeptidase

Table 4 *Sequential measurements of bile flow (µl min⁻¹ g⁻¹ wet liver weight) and bile salt excretion (µg min⁻¹ g⁻¹ wet liver weight) in control and TPN-treated animals before and in response to intraportal taurocholic acid infusion and during secretin infusion*

	Bile flow		Bile salt excretion	
	Control	TPN	Control	TPN
Basal	0·49±0·02	0·34±0·08	6·48±2·5	4·61±1·66
Taurocholic acid infusion (µmol min⁻¹ kg⁻¹)				
1·0	0·63±0·08	0·40±0·15	7·76±3·2	4·86±1·8
2·0	0·77±0·13	0·56±0·15	11·96±3·5	7·99±2·28
5·0	1·21±0·21	0·68±0·16	23·75±5·31	11·50±4·49
10·0	1·86±0·30	0·70±0·20	44·44±9·10	13·72±5·30
20·0	2·24±0·28	0·61±0·25	65·36±10·34	13·00±4·70
Secretin (2 units min⁻¹)				
First 10 min	2·28±0·22	1·40±0·48	16·67±6·16	15·63±5·0
Second 10 min	2·40±0·38	1·56±0·43	9·38±3·7	9·83±5·3

Values are means±s.d.

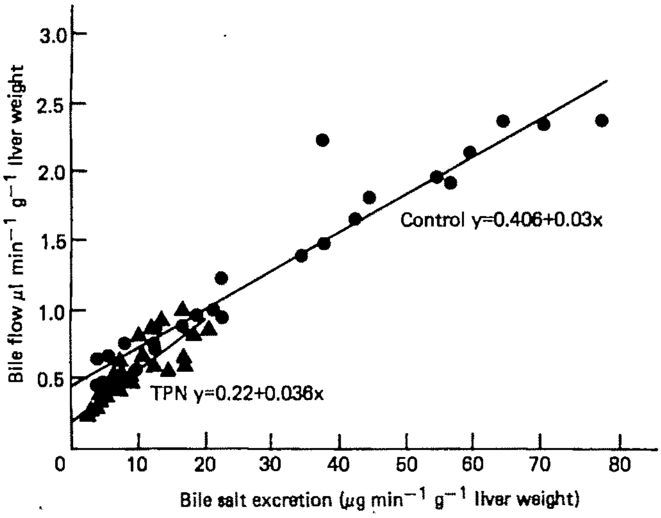

Figure 1 *The relationship between bile flow and bile salt excretion in control (●, y=0·406+0·03x) and TPN-treated (▲, y=0·02+0·036x)*

pigs receiving TPN therapy, varying quantities of green, mucous-like sludge were found in the gallbladder. Microscopic examination demonstrated amorphous conglomerates containing pigment, presumably calcium bilirubinate, but there was no crystal formation[27]. There was no light microscopic evidence of cholecystitis in either group. Serial liver function tests did not vary either within or between the two groups over the study period (*Table 3*).

There was a significant decrease in basal bile flow ($P<0{\cdot}01$) and basal bile salt excretion ($P=0{\cdot}028$) in the TPN group (*Table 4*). Following intra-portal TCA infusion there was a significantly increased response of bile flow and bile salt excretion in all animals. In the TPN animals, the magnitude of this response for both bile flow and bile salt excretion was significantly reduced as compared to the controls (*Table 4*). The maximal response to TCA in the TPN group was achieved at a rate of infusion of 10 µmol kg⁻¹ min⁻¹ and thereafter there was no further response to incremental TCA infusion. This contrasts to the response of the control pigs in which no plateau was achieved over the range of TCA infusion (*Table 4*).

In both groups there was a significant positive correlation between flow and bile salt excretion (controls: $r=0{\cdot}97$, $P<0{\cdot}001$; TPN: $r=0{\cdot}87$, $P<0{\cdot}01$). There was no significant difference between the two groups in the slope of the regression lines but the intercept, representing the bile salt independent fraction of bile flow[28], was significantly lower in the TPN group ($P<0{\cdot}05$) (*Figure 1*).

Intraportal secretin infusion produced a significant increase in bile flow in all animals. Since there was no significant difference between the first and second bile volumes within each group, these data were pooled and expressed as a percentage increment of basal bile flow. When so expressed there was no significant difference between the TPN and the control group.

During the bile flow studies there was no variation in blood pressure, blood gases or rectal temperature in any animal. All recordings remained within the range for pigs of comparable age as previously established in our laboratory.

Discussion

We have demonstrated the establishment of a TPN model in which adequate nutrition has been maintained using a clinical TPN regime. An important feature of this model is that two hepatobiliary complications of TPN therapy, i.e. gallbladder sludge and cholestasis, have occurred in all treated animals. To our knowledge this is the first report of consistent gallbladder sludge formation in a TPN animal model.

Several species have been used in the development of TPN animal models, but each has certain deficiencies. The monkey model[29] is phylogenetically more appropriate to man but monkeys are expensive, difficult to obtain and are easily stressed when restrained. The rat model[30,31,32] has been widely adopted and, although it is less expensive and easier to house and handle, a custom made infusion regime is required which differs from the clinical formulations. The rat has no gallbladder and gastric ulceration has been reported as a complication of intravenous alimentation[33]. Most of the small species, including the rabbit, the guinea-pig and the prairie dog are strict herbivores, so that bile salt handling and gastrointestinal function are dissimilar to man[34]. Although the major bile salt excreted in the pig differs from that of man, bile salt handling[33] and gastrointestinal function[35] are similar.

The pig has a number of features which make it particularly suitable. Unlike the dog and the monkey, the pig is not a carrier of chronic liver disease[36] and it has similar liver function to man and comparable nutritional requirements[16,17,20]. It is sufficiently docile to permit easy handling, and in the present experiment there was no discernible stress response.

Another important feature of the model is that TPN has been successfully administered to a young animal undergoing rapid growth. Most other experimental studies have used an adult animal. As hepatobiliary dysfunction is more common in pediatric patients receiving TPN, this model has particular relevance.

Although there was no abnormality in the routine liver function tests, nor evidence of cholestasis on light microscopy of liver biopsy material, a pathophysiological state of cholestasis, by definition a decrease in bile secretion[37], existed. Basal bile flow and bile salt excretion were significantly reduced, and the ability of the liver to respond to a bile salt stimulus was impaired. Persistence of these changes might result in the development of histological and biochemical evidence of cholestasis.

Cholestasis in this model involves not only the bile salt dependent, but also the bile salt independent fraction of bile flow. The similar responses to secretin suggest that the canalicular rather than the ductular component is involved[38]. Hence, in this TPN model both components of canalicular secretion are impaired. A defect in hepatic canalicular function has been postulated previously as the mechanism of TPN-associated cholestasis in the human neonate[39].

Gallbladder sludge occurs in a high proportion of patients receiving TPN and many develop gallstones[5]. Sludge may occur as the result of altered gallbladder motility, or increased bile lithogenicity, or both. The absence of enteral stimulation associated with TPN may alter release of gastrointestinal hormones and, in turn, affect gallbladder motility. Alternatively, it has been suggested that during TPN there is an increase in lithocholic acid due to an alteration in gut microflora and changes in secondary bile salt metabolism.

Whilst at present the reasons for the development of both cholestasis and gallbladder sludge during TPN are unknown, this animal model provided the means for a detailed investigation of all the mechanisms involved. Further studies could include sequential measurement of gut hormone levels, and investigations of bile salt kinetics.

A possible criticism of this pig model is that the growth rate of the TPN animals was less than that in the controls. The pigs were not fed isocalorically, since it is not possible to ensure equal availability of metabolizable energy from dietary sources of different compositions and different routes of administration. An attempt to do so may have nutritionally compromised the controls. The control pigs were fed a diet formulated to achieve optimal growth. Although the growth rate in the TPN groups was less, this is unlikely to reflect a significant nutritional difference as carcass composition in the two groups was comparable. In the TPN group weight gain was within acceptable limits for pigs of this age, and there was no evidence of malnutrition. The similarity in water content in the two groups indicates that the weight gain achieved was not due to water retention.

In summary, a nutritionally competent model of TPN has been established in the growing pig. Adequate nutrition was achieved using a clinical TPN regime. Two of the common hepatobiliary complications of TPN, namely gallbladder sludge and cholestasis, have occurred in all treated animals. This model should provide a useful tool to investigate further the mechanisms of these abnormalities.

Acknowledgements

We would like to thank Dr M. Meerkin and staff of The Prince of Wales Biochemistry Department, for the performance of routine liver function tests; Dr P. Bulpitt for the examination of histopathology specimens; Professor H. Lloyd-Davies and Mr D. Petree for the analysis of carcass composition; Lynda Christie and Diane Grady for their expert technical assistance; Jan Wilson for the preparation of the manuscript.

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Paper accepted 14 February 1987

Br. J. Surg. 1987, Vol. 74, July, 643–644

Ascaris lumbricoides and intestinal perforation

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Intestinal perforation is a common and important cause of abdominal catastrophe. The aetiological factors are numerous, varied and well documented[1–11]. Many authors in the tropics have implicated *Ascaris lumbricoides* as a causative agent in a proportion of these perforations[12–20]. This author has always held a contrary view and, despite a careful search over the past 4·5 years, has not found any evidence to support ascariasis as a cause of intestinal perforation. This review evaluates the available medical literature dealing with this controversial topic.

Lifecycle and properties of Ascaris lumbricoides

The eggs of *Ascaris lumbricoides* are ingested by eating contaminated vegetables. The outer chitinous covering of the eggs is digested by gastric juices to release the small larvae. These larvae pierce the small intestine and enter the blood vessels and lymphatics. Those in blood capillaries are transported via the hepatic vein and inferior vena cava to the heart and thence to the lungs, while those in lymphatics travel via the thoracic duct and subclavian vein. The larvae migrate into the lung alveoli where they undergo maturation and moult twice. They are then carried up the trachea and pass over the epiglottis and down the oesophagus to the stomach and intestine. The journey from the lungs to the intestine takes 10 days during which time the larvae have increased 10 times in size, now measuring 2 mm. They become fully mature in 60 days.

The rhabtidiform larvae have a great propensity to migrate through tissues and may be deposited in the peritoneum forming granulomatous peritonitis, or may develop into adult worms in the peritoneal cavity. The adult worm, however, confines its movement to maintaining its position in the intestine against the propulsive forces that move intestinal content distally.

Ascaris lumbricoides: a cause of intestinal perforation

Even though typhoid enteritis is the commonest cause of intestinal perforation in the tropics[1–4], other causes are frequently encountered. These include amoebiasis, tuberculosis, non-specific ulceration[5,6], perforation secondary to an obstructing lesion, strangulated Richter's hernia[7], trauma, small bowel lymphoma[8], Crohn's disease[9,10], polyarteritis modosa[8], radiation enteritis and such drugs as Slow-K[11].

Despite intensive documentation of these numerous causes of bowel perforation, the protagonists of the hypothesis that *A. lumbricoides* causes intestinal perforation have tended to give the impression that once typhoid enteritis has been excluded, then there is a cause and effect relationship between any ascarid found in the peritoneum and bowel perforation[12–20]. Ascarid worms have been found passing through various types of ulcers including typhoid perforations, but the majority have been described in relation to non-specific ulcers. This is hardly surprising as the latter are the third commonest cause of intestinal ulcers in the tropics[4,8]. Since 35–90 per cent of children in the tropics are infested with *A. lumbricoides*[14], one might expect to find worms migrating through perforations in the intestine caused by non-specific ulcers in the majority of cases.

As stated above, the ascarid larva can penetrate tissues and may become deposited in the peritoneal cavity from where it may develop into adult worm. This could explain why the ascarid worm is occasionally found in the peritoneal cavity without any evidence of bowel perforation[21]. Considering the large number of people infested with *A. lumbricoides*[14] in comparison with those with typhoid fever[1,22], perforation attributed to *A. lumbricoides* would be expected to be more than that due to typhoid fever. However, the converse is the case.

A. lumbricoides resides mostly in the middle third of the jejunum but perforations attributed to this parasite have been described mostly in the terminal ileum[12–17,23] and the caecum[18] and to date no case of jejunal perforation has been attributed to *A. lumbricoides*.

The intestine has an immense capacity for dilatation. It has been claimed that it can accommodate 5000 worms without symptoms occurring[24]. It is thus unlikely that direct pressure by ascarids can produce intestinal perforation as claimed by some authors[14], except in confined spaces such as the appendix, Meckel's diverticulum[25] and the common bile duct[26]. Under normal circumstances, *A. lumbricoides* resides in the small intestine. When the environment in the intestine becomes unfavourable such as during starvation, inflammation and obstruction, the ascarid will migrate to other less hostile parts. They may thus migrate into the biliary system, the pancreatic duct, the stomach to be vomited through the mouth, into nasogastric tubes causing blockage, into the peritoneum through perforated ulcers or anastomotic suture lines, or through the anus. They may convert near perforations caused by typhoid, amoebiasis, tuberculosis and non-specific ulcers into frank perforation, but it is unlikely that they produce direct perforation of the intact intestine. It is of interest that perforation would in any case be deleterious to the species since it does not survive for long outside the intestinal lumen[27].

Perforations are occasionally encountered in the intestine for which no aetiology is apparent. In a review of 54 cases at the Royal Infirmary in Edinburgh, Dixon *et al.* found that in eight cases (15 per cent) no aetiology could be found[8]. In an unpublished study from the University of Calabar Teaching Hospital, Nigeria, the author has found few such cases of intestinal perforation of unknown aetiology. These perforations could easily constitute exit foramina for ascarids escaping from unfavourable intestinal conditions and some surgeons might unwittingly incriminate *A. lumbricoides* as the culprit.

From the above evidence it would seem reasonable to conclude that *A. lumbricoides* may cause perforation of diseased and ulcerated intestine as in amoebiasis, typhoid and in non-specific ulceration, and that it may cause pressure necrosis when trapped in confined spaces such as the appendix, pancreatic duct, common bile duct and Meckel's diverticulum. However,

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this author is forced to agree with Davey[23] and Edington *et al.*[27] that it is unlikely that *A. lumbricoides* can perforate normal healthy intestine.

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Paper accepted 2 February 1987

Case reports

Br. J. Surg. 1987, Vol. 74, July, 645–646

Enterovesical fistula due to a Dacron aortic graft

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The occurrence of an aorto-enteric fistula at the suture line between an arterial prosthesis and the aorta is a well recognized complication which occurs in up to 2 per cent of aortic grafts[1,2]. In rare instances the body of an arterial prosthesis may erode into bowel giving rise to a 'paraprosthetic–enteric' sinus[3] which does not communicate directly with the bloodstream. An extreme example of this process has been described in which a polytetrafluoroethylene (GORE-TEX*) graft inserted between the aorta and hepatic artery was found lying entirely within the lumen of the duodenum[4]. This phenomenon has been called 'cannibalization' and we describe here an enterovesical fistula caused by a Dacron® prosthesis eroding through the wall of the ileum.

Case report

A 72-year-old man presented with a 3 month history of dysuria, nocturia and cloudy urine. Four years previously he had undergone elective repair of an aortic aneurysm, in which a Dacron bifurcation graft was anastomosed proximally to the abdominal aorta and distally to the common femoral arteries. Twelve separate mid-stream specimens of urine were cultured in a 2 month period, and *Escherichia coli*, *Proteus* spp. or *Klebsiella* spp. organisms were grown from each one, despite almost continuous antibiotic therapy. A clinical diagnosis of vesico-intestinal fistula was made and cystoscopy carried out. This examination revealed the typical appearances of a fistula, located on the right posterolateral wall of the bladder. The orifice of the fistula was cannulated and contrast medium injected (see the radiograph and diagram shown in *Figure 1*). The cannula was seen angulated downwards alongside the right 'limb' of the Dacron prosthesis. Contrast medium was seen to outline the prosthesis and fill several loops of small bowel. A biopsy of the fistula was taken.

At operation a 6 cm length of prosthesis was found to have eroded through the bowel wall and it was lying entirely within the lumen of the ileum. The bladder was firmly adherent to the involved segment of bowel and a small abscess was present. The infected graft was removed, the aorta ligated and circulation to the legs restored by an axillobifemoral graft. The bladder was separated from the bowel but because the fistula into the bladder was small no repair was undertaken. Catheter drainage of urine was instituted. A 15 cm length of ileum was resected. Postoperatively the patient developed synergistic gangrene of the abdominal wall which was fatal.

Histology of the small bowel and the bladder biopsy revealed no underlying lesion which might otherwise have explained the enterovesical fistula. Bacteriological cultures of the Dacron graft and surrounding pus both grew mixed faecal flora.

Discussion

An enterovesical fistula has not previously been described in association with an aortic graft. The sequence of causative

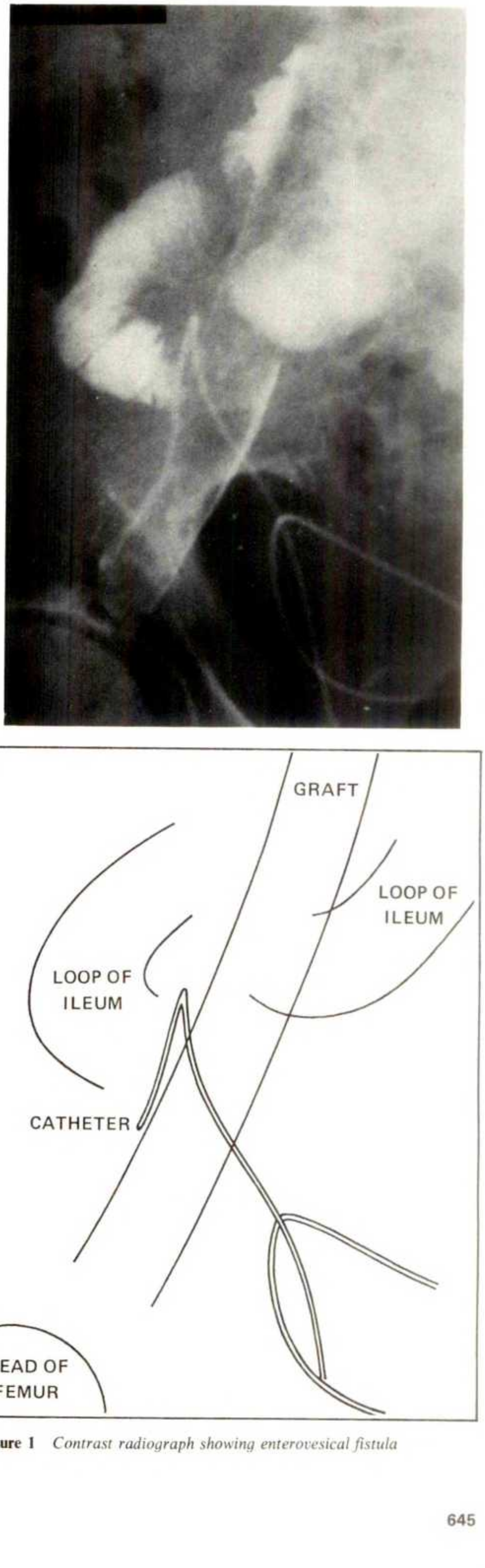

Figure 1 *Contrast radiograph showing enterovesical fistula*

events was probably as follows: adherence of the ileum to the graft with subsequent penetration of the bowel by the graft; then sepsis around the eroded bowel which would have given rise to an abscess which in turn 'pointed' into the bladder.

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* *Trademark of W. L. Gore & Associates Inc.*

Erosion of the bowel by an arterial prosthesis is a complication which is not confined to the area of the anastomosis, and it seems likely that it may occur if a prosthesis is not adequately protected by a covering of peritoneum.

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Paper accepted 1 September 1986

Case reports

Br. J. Surg. 1987, Vol. 74, July, 646

Infected Charnley hip prosthesis presenting as a perianal sinus

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Patients with perianal discharge present frequently to general surgeons. We report an unusual case in which a perianal discharge occurred secondary to an infected hip prosthesis.

Case report

A 73-year-old man was referred to the general surgical outpatient clinic with a 12 month history of perianal discharge sufficient to soil his clothing. He had no other gastrointestinal symptoms and his general health was excellent. Bilateral Charnley arthroplasties had been performed in 1970 and 1972. In 1977 he fractured the shaft of the right femur and the right hip prosthesis was subsequently replaced. Superficial abscesses in his thigh wound were drained in 1980 and 1983 and culture of the pus grew *Escherichia coli* and *Bacteroides*. He remained ambulant and pain free. No recurrence of his thigh abscesses occurred, nor did a sinus persist in the area of the thigh wound.

On examination a cutaneous opening was identified 3 cm from the anal verge at the 11 o'clock position. Rectal examination and sigmoidoscopy were normal.

He was admitted for examination under anaesthesia which revealed a long sinus tract with no apparent communication with the bowel. No operative procedure was performed, and a sinogram was obtained (*Figure 1*); this revealed that the sinus communicated with the hip joint. Bacteriological swabs from the tract grew *E. coli* and *Bacteroides fragilis*.

Since the patient was otherwise asymptomatic, no further surgical intervention was undertaken.

Discussion

The majority of patients who present with persistent discharge from a lesion in the perianal region have a low fistula-in-ano. These patients are easily treated by laying open the fistulous tract having confirmed that the internal opening is below the anorectal ring[1]. In this patient the presence of a high fistula-in-ano was suspected at examination and a sinogram revealed the unusual cause of the discharge.

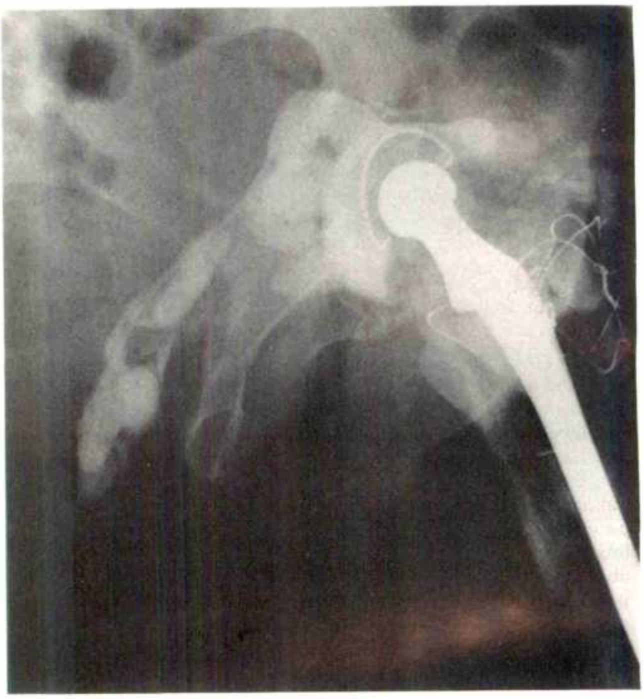

Figure 1 *Sinogram of right hip joint (oblique view) showing communication of perianal sinus with joint cavity*

The mechanism of this rare presentation is not entirely clear. The presence of cement in the pelvic cavity and the growth of organisms of gastrointestinal origin from both the perianal sinus and the previous thigh abscesses suggests that the bowel was damaged at the second hip operation. Only one previous case of perineal infection associated with an infected prosthetic hip joint has been reported[2]. The patient presented with an ischiorectal abscess and two features of the case would support the contention that bowel damage was the cause of the infection. Firstly, the ischiorectal abscess was associated with protrusion of the acetabular component of the prosthesis, and secondly, a faecal fistula discharged from the thigh wound following the removal of the prosthesis. We believe that in these two cases minor damage to the bowel during hip surgery caused the formation of an abscess which then tracked down to the perineum. Recognition of this rare complication avoids meddlesome anorectal surgery.

Acknowledgements

Thanks are due to Mr C. S. McArdle and Mr A. B. Young for allowing us to report this case and to Mrs W. Hughes for typing the manuscript.

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Paper accepted 10 September

0007–1323/87/070646–01$3.00

Br. J. Surg. 1987, Vol. 74, July, 647

Cerebral metastases from occult papillary carcinoma of the thyroid

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lt papillary thyroid carcinomas are by definition small pable lesions a few millimetres in diameter which rarely tasize widely although involvement of local cervical lymph can occur. We report the first documented case of a who presented with a cerebral metastasis from an occult tumour measuring <3 mm in diameter.

port

-old Egyptian wrestler presented with frontal headaches, sion in the right eye and a tendency to walk into objects on ne only neurological abnormality detected was a dense right us hemianopia with flat discs. No abnormal signs were general examination.

ematological and biochemical screening was normal, as was tology, chest X-ray and urine analysis. A CT scan of the brain mass lesion of mixed attenuation in the posterior pole of the tal lobe suggestive of a primary tumour. At craniotomy, a bbery nodule was excised from the left occipital pole.

logy revealed papillary carcinoma (*Figure 1a*). Investigation of oid was then undertaken which demonstrated a 1·5 cm le nodule in the left lobe of the thyroid gland which was solid und and showed no uptake on radio-iodine scan; the right normal on scanning. A CT scan of the neck, thorax and en was normal. The thyroid was explored and a left lobectomy ned but frozen section showed the lesion to be a benign follicular enoma. The right lobe was then removed though no abnormality could be detected. Subsequent sectioning showed several small benign follicular adenomata and on more extensive sectioning two of these showed foci of papillary carcinoma, the larger measuring 3 mm in width. Histological appearances were identical with those of the cerebral lesion (*Figure 1b*). Postoperative treatment has involved suppressive doses of thyroxine, high dose radio-iodine administration and radiotherapy to the posterior cranial fossa.

Six months later the patient presented with a further deposit in the right frontal lobe and he is at present undergoing further radiotherapy.

Discussion

The autopsy prevalence of occult papillary thyroid carcinoma (which varies markedly from the clinical prevalence) depends on the population under study, environmental factors and the diligence of the histological search as reflected by the thickness of successive sections through the gland[1]. The prevalence varies between 2·8 and 13·0 per cent in American studies[2–4] and is as high as 17·9 per cent in a Japanese study of patients previously exposed to nuclear radiation[5]. Despite a high prevalence, occult papillary lesions are relatively benign. Cervical metastases may occur but distant metastases are rare[6]. In a detailed autopsy study from Japan[7] only 20 of 128 patients (16 per cent) were found to have cervical node metastases from occult thyroid carcinoma and in only one case did the tumour cause death owing to widespread dissemination to the abdominal viscera and bones but not the brain. A further 570 patients with occult papillary carcinoma in whom nodes were not available for assessment lived a normal life span without manifestation of their disease.

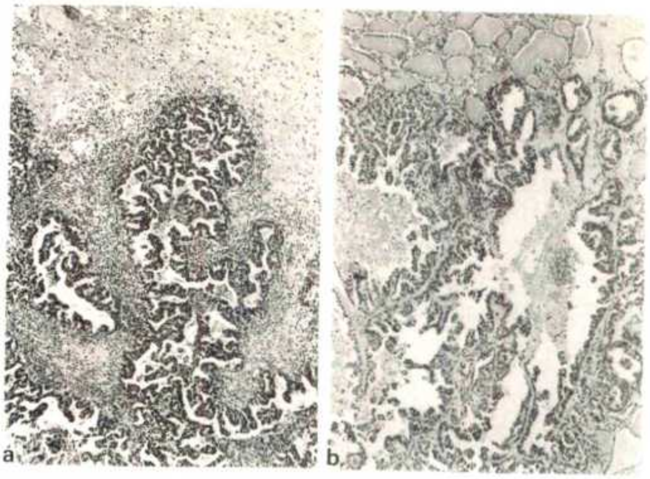

Figure 1 **a** *Photomicrograph of part of the cerebral metastasis showing moderately well differentiated papillary adenocarcinoma (haematoxylin and eosin × 80) with a similar histological appearance to* (**b**), *the small occult papillary carcinoma of the thyroid (haematoxylin and eosin × 80)*

There has been one report of metastases from an occult papillary carcinoma in the vertebral column[8] but in general this tumour is harmless and thus is unlike other thyroid cancers which more readily metastasize or infiltrate locally. There have been no previous reports of a tumour behaving in the manner described and whilst this may be a freak occurrence it demonstrates that the thyroid gland cannot be excluded as the primary source of metastatic carcinoma until the whole gland is available for thorough histological examination.

Acknowledgements

We acknowledge the helpful advice of Dr A. W. Boylston and Mr R. Hayward, Dr N. Francis for preparation of photomicrographs and Miss M. Petrie for typing the manuscript.

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Paper accepted 11 September 1986

0007-1323/87/070647-01$3.00

Case reports

Br. J. Surg. 1987, Vol. 74, July, 648

Obstructing calculous material in a periampullary duodenal diverticulum associated with primary common bile duct calculi and acute pancreatitis

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Periampullary duodenal diverticula are usually asymptomatic but may be associated with an increased incidence of abnormalities of the pancreatic or biliary tree. We report a patient presenting with acute pancreatitis and subsequently obstructive jaundice associated with calculous material filling a periampullary diverticulum together with primary common bile duct calculi, all of which were successfully removed endoscopically.

Case report

A 69-year-old woman was admitted as an emergency with a 12 h history of abdominal pain and vomiting. On examination there was epigastric tenderness and an irreducible tender right femoral hernia. White blood count was elevated at 16.5×10^9/l with 90 per cent neutrophils and serum amylase was 2067 units/l, indicative of acute pancreatitis.

The patient improved with intravenous fluid therapy and antibiotics and was transferred to theatre for femoral hernia repair during which the peritoneal cavity was opened to allow exploration of the upper abdomen. The hernia contained viable omentum and the abdominal cavity contained clear ascitic fluid with an amylase concentration of 6955 units/l. The pancreas was swollen and oedematous and the biliary tree distended but no stones were palpable.

Ultrasound examinations confirmed a dilated biliary tree with pancreatic swelling consistent with acute pancreatitis, but no biliary calculi were identified. Recovery was complicated by obstructive jaundice (bilirubin 194 μmol/l), respiratory failure, protracted ileus and haematemesis but the patient was well enough for discharge home after 29 days.

Six weeks later elective endoscopic retrograde cholangiopancreatography (ERCP) was performed with antibiotic cover when liver function tests had almost returned to normal. At duodenoscopy the papilla was thought to be completely within a 2·5 cm diameter duodenal diverticulum which was full of soft tenacious material very similar in consistency to a primary bile duct calculus (*Figure 1*). This was removed with a combination of dormia basket extraction and irrigation to expose the papilla thus enabling endoscopic retrograde cholangiography which revealed an 8 mm diameter common bile duct containing three calculi at its lower end. These calculi were successfully extracted after endoscopic sphincterotomy and were identical in colour and consistency to the material filling the diverticulum. There were no visible calculi in the gallbladder. The patient remains symptom-free 6 months later.

Discussion

Duodenal diverticula are a common finding at ERCP and are usually asymptomatic. Complications are rare but diverticulitis, haemorrhage, perforation, duodenal obstruction, formation of enteroliths, neoplastic change and malabsorption have all been

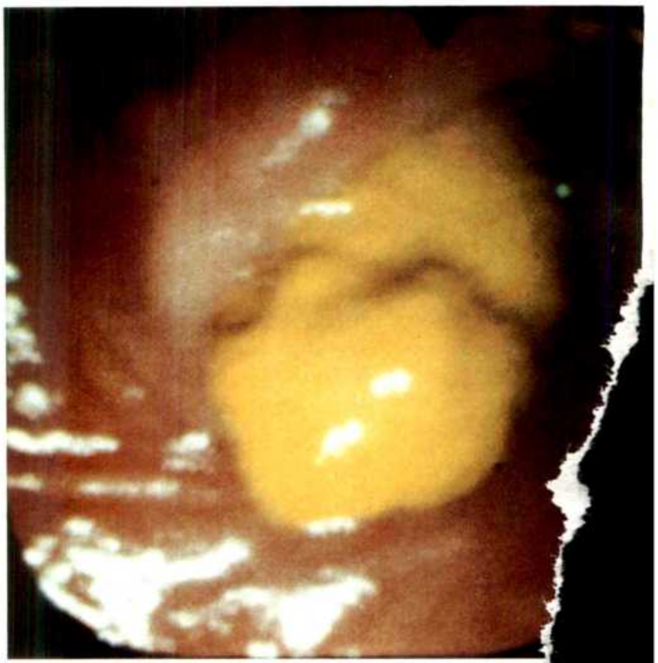

Figure 1 *Endoscopic view of duodenal diverticulum contain*
of the same colour and consistency as the calculi in the com

reported. Periampullary diverticula are associa
increased incidence of abnormalities of the par
biliary tree and in particular cholelithiasis[1]. This n
to stasis either from compression of the common
papillitis, but Lotveit demonstrated that the diver
more likely to render the sphincter mechanism i
leading to reflux and ascending infection with β-gluc
producing bacteria predisposing to calcium
calculi[3]. Surgical options for periampullary
associated with recurrent biliary or pancreatic dise
diverticulectomy, sphincteroplasty, choledochoduo
choledochojejunostomy, 'diverticulization' (Billr
trectomy with vagotomy) and duodenojejunostoı
carry a significant mortality and morbidity. Our pat
unusual complication of material with the consistency
primary bile duct calculus completely filling the diverticul
with similar calculi in the lower common bile duct. This caused a severe attack of acute pancreatitis associated with obstructive jaundice. The diverticulum and common bile duct were successfully cleared endoscopically and surgery is not contemplated.

Acknowledgements

We would like to thank Denise Huckerby for typing the manuscript.

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Paper accepted 25 November 1986

Br. J. Surg. 1987, Vol. 74, July, 649

Cryptogenic Candida albicans cholecystitis

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meta
nodes t with biliary candidiasis illustrates the consequences of
patient us in association with biliary mud in the elderly
thyroid person.

Case re ort

A 47-yea old woman was admitted with a tender mass in her right
impaired v rant. The patient was known to have cholelithiasis, with
the right. T odes of biliary colic, a history of severe coronary artery
homonymo diabetes mellitus. Abdominal ultrasonography
detected on an enlarged, thick-walled gallbladder with numerous
Full ha extra- and intra-hepatic bile ducts were not dilated. The
sputum c tion was stable and she was afebrile with a normal white
revealed a and serum bilirubin.
left occipi of cystic duct obstruction, in the face of severe cardiac
2·5 cm ru on, the patient underwent a cholecystostomy, performed
Histo naesthesia. At surgery, odourless white bile was drained.
the thy friable pigmented stones were extracted from the
impalpab These stones were not analysed. The patient was started on
on ultras chloramphenicol. Bile cultures, taken from the gallbladder
lobe wa ry, grew *Candida albicans* as the sole pathogen; the
abdom tment was discontinued, but antifungal treatment was not
perfor Additional bile cultures grew *Candida albicans*, whereas
n from urine, sputum and blood were all *Candida* free.
ient made an uneventful recovery, and was discharged with a
cystostomy Foley catheter draining about 300 ml of bile daily.

Three months after surgery the patient was admitted for evaluation of her cholecystostomy. A cholangiogram performed via the cholecystostomy tube visualized a round filling defect in the gallbladder with good passage of contrast medium into the common bile duct and duodenum (*Figure 1*). A gallstone was extracted through the cholecystostomy tract using a Dormier's basket. The stone, which looked macroscopically identical to those stones removed from the gallbladder during the initial procedure, was analysed and found to be composed of inspissated bile, invaded by hyphae of *Candida albicans*.

No antifungal treatment was administered, and the patient was discharged after the procedure with the cholecystostomy drain in place. Four months later, bile was still draining, with bile cultures positive for *Candida albicans*; however, the patient has remained asymptomatic.

Discussion

Candida albicans is a commensal in the human mouth, gastrointestinal tract and vagina. Under changing host conditions, fungal infection may proliferate and disseminate to remote organs. Debility, diabetes mellitus and prolonged antibiotic or steroid treatment are the main contributing factors. The common portals of entry are: parenteral nutrition lines, burn wounds, urinary system and migration across the gastrointestinal tract[1,2].

Biliary tree involvement with *Candida albicans* infection is a rare occurrence. The cases reported in the past were secondary to surgery or invasive procedures performed on the biliary system or alimentary tract. Marsh *et al.*[3] reviewed 55 surgical patients who suffered postoperatively from *Candida* infection, including 5 patients with candida positive bile culture. Forty-five patients of the series underwent abdominal surgery. Of these, six had invasive procedures performed upon the biliary system: cholecystectomy in one, biliary diversion in two, and transhepatic cholangiography in three patients.

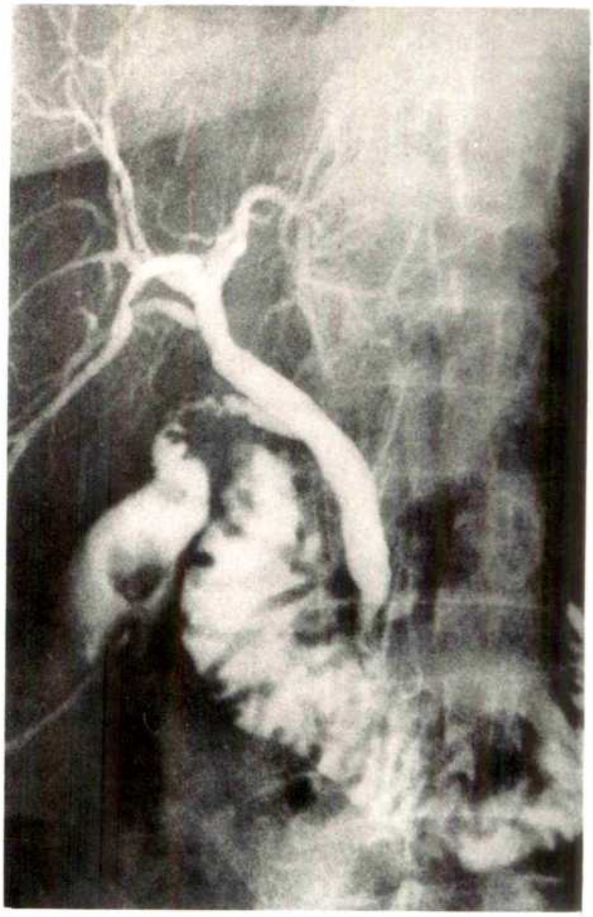

Figure 1 *Cholangiogram visualizing the fungus ball as a round filling defect in the gallbladder. Good passage is demonstrated through the common bile duct into the duodenum*

Uflacker *et al.*[4] presented a patient with massive proliferation of candida in the common bile duct following cholecystectomy and T-tube drainage. A study on fungal sepsis in 65 surgical patients, by Burchard *et al.*[5] revealed 7 patients with dissemination of *Candida albicans*, of whom one had colonization in the gallbladder.

Our case was unique for lack of invasive procedure involving the biliary system before the gallbladder colonization with *Candida albicans*. Diabetes mellitus was the only predisposing factor for *Candida albicans* proliferation. No *Candida* infection in any other organ system, nor sepsis were reported from her past history, to substantiate the assumption of remote dissemination, and the portal of entry has remained an enigma. *Candida albicans* infestation in the gallbladder presented as fungus balls, diagnosed as 'stones' which obstructed the cystic duct, and necessitated acute drainage of the gallbladder. The potential of fungus material to occlude the biliary canals is noteworthy[4].

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Paper accepted 11 December 1986

0007–1323/87/070649–01$3.00 © 1987 Butterworth & Co (Publishers) Ltd

Br. J. Surg. 1987, Vol. 74, July, 650

Effects of knee flexion on the in situ femoropopliteal vein bypass graft

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In situ vein bypass grafting in the femoropopliteal segment has increased in popularity in recent years and the technique may have advantages when the graft is inserted into a crural vessel[1]. In contrast to the situation with reversed vein bypass grafts, the unexpected observation has emerged that *in situ* grafts inserted on a crural vessel have a similar or better patency rate than those inserted on the popliteal artery[2]. We offer a possible explanation for this from a prospective 1 year follow-up of 26 below-knee *in situ* femoropopliteal grafts. We also studied femorocrural grafts and reversed-vein femoropopliteal grafts.

Each graft was assessed by clinical examination, ankle Doppler pressures and intravenous digital subtraction angiography with the knee in extension and flexion at 1 week, 3 months, 6 months and 1 year after implantation. None of the grafts had stenosis on the operative arteriogram and postoperative digital subtraction angiography revealed that the graft gently curved into the popliteal fossa when the knee was extended. However, as the knee was flexed most grafts developed considerable tortuosity (*Figure 1*). Despite this, the resting ankle pressures were unaffected by knee flexion in every case; a finding that concurs with a study of reversed vein and PTFE grafts[3]. One of our grafts developed a stenosis at the site of angulation one year later and this coincided with a recurrence of mild claudication and a drop in postexercise ankle Doppler pressure index from 1·1 to 0·75. The stenosed segment was removed and replaced with autogenous vein; on histological examination it revealed severe myointimal hyperplasia. The stenosed segment was not related to a tendon or the medial head of gastrocnemius. When performing a bypass using *in situ* vein to the distal popliteal artery we ensure a smooth curve as the graft enters the popliteal fossa. However, there may be an acute angulation of the graft on flexion that is deleterious to long-term patency (*Figure 2*). We did not observe this angulation in studies of reversed vein grafts routed through the subsartorial canal or in *in situ* grafts inserted beyond the popliteal artery.

We consider that there are advantages to the *in situ* technique in femorocrural reconstruction but that these are counterbalanced by the problem of angulation when the graft is inserted into the infragenicular popliteal artery.

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Paper accepted 20 October 1986

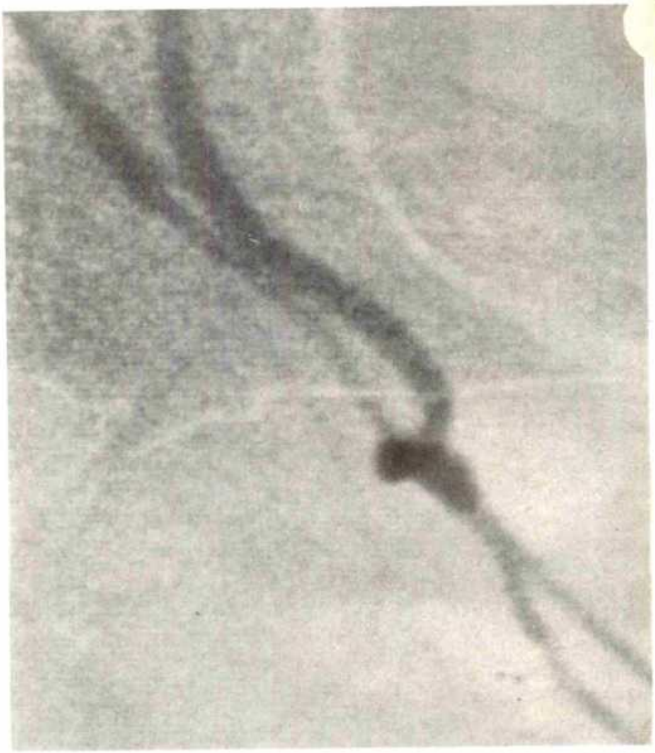

Figure 1 *Intravenous digital subtraction angiography 1 week after insertion of graft with leg flexed*

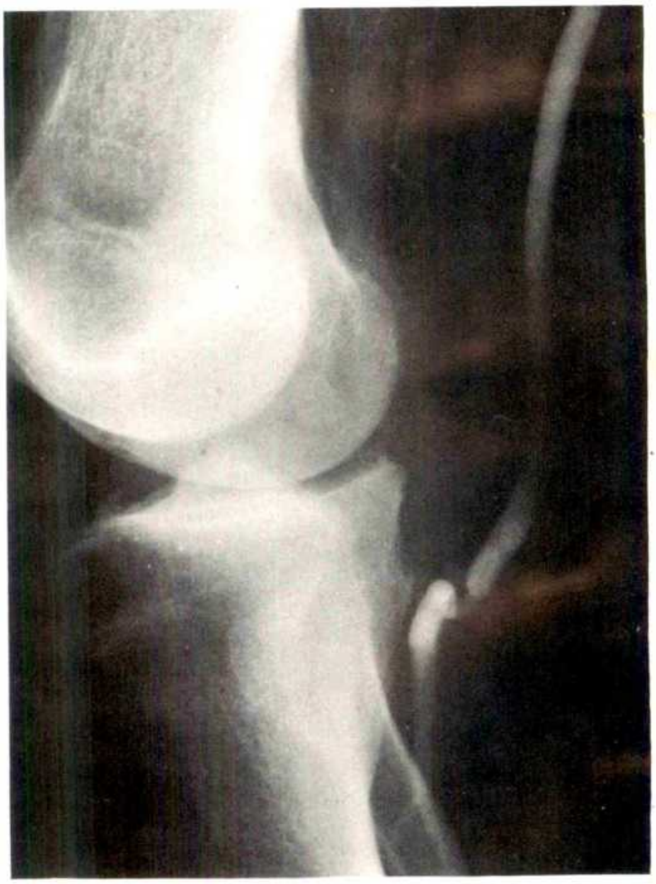

Figure 2 *Arteriogram 1 year later showing stenosis due to subintimal hyperplasia at the site of the previous kinking*

Br. J. Surg. 1987, Vol. 74, July, 651

Upper dorsal sympathectomy for palmar hyperhidrosis

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Severe palmar hyperhidrosis may cause significant social and psychological problems for the patient. The results of conservative measures such as anticholinergic drugs, sedatives, antiperspirant creams, psychotherapy and iontophoresis are generally disappointing[1]. Sympathetic denervation abolishes eccrine secretions and thus gives long lasting relief of symptoms.

This paper details our experience over a 10 year period with upper dorsal sympathectomy for palmar hyperhidrosis.

Patients and methods

Between January 1974 and February 1984, 135 upper dorsal sympathectomies were performed in our unit for primary palmar hyperhidrosis. There were 60 female and 15 male patients, who ranged in age from 7 to 49 years with a mean age of 23·5 years.

Main symptoms were either profound social embarrassment or interference with employment. Surgery was recommended only after the failure of conservative measures. All patients were investigated preoperatively to exclude a secondary cause for their condition.

Bilateral sympathectomies were performed on 65 patients (86·6 per cent); in 62 patients a staged procedure was used.

Upper dorsal sympathectomy was performed via a supraclavicular approach using the method described by Telford[2].

In 131 operations the sympathetic chain was divided from the lower portion of the stellate ganglion to the third thoracic ganglion, in the remaining four cases the second and third thoracic ganglia were removed only. Metallic clips were used to secure haemostasis and to mark the divided ends of the sympathetic chain. Successful sympathectomies were confirmed by frozen section of all cases.

Results

All patients were reviewed regularly. The period of review ranged from 2 months to 7 years with a mean of 6 months.

In 71 cases (94·6 per cent) the patients were completely satisfied with the results of their surgery. Four patients (5·4 per cent) were less than satisfied, of these two female patients had residual sweating along the ulnar border of the palm. One male patient required a second operation which was successful. The remaining patient was found to have an underlying psychiatric complaint.

There were no operative deaths. Postoperative complications were seen after 14 procedures (10·3 per cent). Three pneumothoraces were noted, only one of which required external drainage. A small chylothorax following a left sided sympathectomy resolved spontaneously. There was one wound infection which responded to antibiotic therapy. Horner's syndrome occurred in nine patients (6·6 per cent). In seven patients this had completely resolved within 2 weeks. The incidence of permanent Horner's syndrome was 1·4 per cent. Both cases occurred early in the series; in recent years no cases of Horner's syndrome have occurred.

The cosmetic appearance of the wound was considered satisfactory in all cases. There were no cases of neural pains in the chest or upper arms. The 'gustatory' phenomenon did not occur. Compensatory hyperhidrosis was not a problem.

The majority of patients were discharged from hospital on the second postoperative day.

Discussion

Despite its distressing nature, primary palmar hyperhidrosis is a benign condition; surgery should only be recommended after the failure of conservative measures. Many different approaches to the upper dorsal sympathetic chain have been described[4].

We prefer the supraclavicular approach as described by Telford[2]. This gives adequate exposure of the upper dorsal sympathetic chain allowing the surgeon to denervate the hand completely whilst preserving the stellate ganglion. Intraoperative frozen sections are performed to confirm the presence of ganglionic cells in the operative specimens; this removes the possibility of operator error in identifying the sympathetic ganglia.

The presence of the inconsistent nerve of Kuntz which forms an alternative pathway for sympathetic fibres to the ulnar nerve is a possible explanation for the residual sweating seen in two of our patients. One patient dissatisfied with her operation was noted subsequently to have a severe anxiety disorder; this emphasizes the importance of excluding other causes of hyperhidrosis before a patient is considered for surgery[5].

On review 94·6 per cent of our patients were completely satisfied with their treatment. These results are encouraging and we recommend upper dorsal sympathectomy using a supraclavicular approach for patients in whom conservative measures have been unsuccessful.

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Paper accepted 24 November 1986

0007–1323/87/070651–01$3.00

Case report

Br. J. Surg. 1987, Vol. 74, July, 652

Development of a false aneurysm following percutaneous transluminal angioplasty

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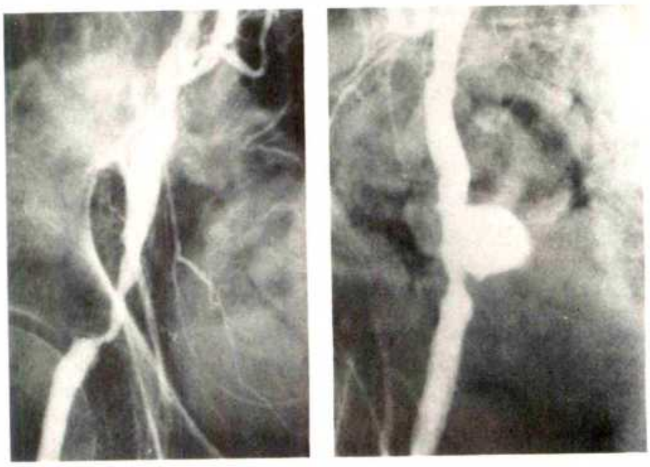

Figure 1 *Arteriograms demonstrating stenosis of the external iliac artery and the same vessel 6 weeks after angioplasty*

Percutaneous transluminal angioplasty is an increasingly used alternative to vascular surgery in the treatment of obstructive arterial disease[1]. Its mechanism depends on splitting atheromatous plaque (if present), intima and, to some extent, the media[2]. Surprisingly arterial rupture is a rare complication[3] and false aneurysm at the angioplasty site has been reported in only two previous cases[4]. An additional case of false aneurysm formation following percutaneous transluminal angioplasty is presented.

Case report

A 66-year-old diabetic man, anticoagulated for rheumatic heart disease, presented with a 3 week history of rest pain in the right foot. On examination there was pre-gangrene of the right foot with evidence of femoropopliteal occlusion.

Arteriography showed two localized stenoses in the right external iliac artery. The superficial femoral artery was occluded throughout its length. Run-off being poor, he was not considered suitable for distal vascular reconstruction. To improve flow to the leg through the profunda femoris, percutaneous transluminal angioplasty was performed via a right femoral approach. The iliac stenoses were dilated twice with an 8 mm inflated diameter, 4 cm long polyethylene balloon on a 7F shaft using inflation pressures of 6 atmospheres and inflation times of 30 s.

The British corrected ratio was 2·9 immediately before the procedure and 5000 units of heparin were given during it. A 40 mmHg systolic pressure gradient across the lesion was reduced to zero by the angioplasty but there was no improvement in the foot which, during the following 6 weeks, progressed to frank gangrene. Repeat arteriography showed that the previous iliac stenoses were widely patent but at the site of angioplasty there was now an aneurysm of the external iliac artery (*Figure 1*).

A below knee amputation was performed. After 3 weeks the patient's general condition improved sufficiently to allow surgical repair of the aneurysm. At operation the vessel was so grossly calcified that proximal clamping was precluded. Proximal control was obtained with an occlusion balloon catheter. There was a 2 cm longitudinal split in the arterial wall and an associated false aneurysm. The disrupted segment of artery was replaced by a short inlay tube of 8 mm Vascutek. Following this the patient made a good recovery.

Discussion

At the University Hospital of Wales percutaneous transluminal angioplasty has been performed on 143 patients with peripheral vascular disease. Complications have occurred in 16 cases (11 per cent). These include: haematoma formation (5 per cent), bradycardia (2 per cent), intimal dissection (1·3 per cent) and emboli (2 per cent). False aneurysm formation at the angioplasty site has been found in only 1 case (0·6 per cent) but follow-up angiography is not routine after angioplasty and therefore the true incidence is unknown.

Local factors which may contribute to the formation of false aneurysm include balloon volume, pressure and duration of inflation, as well as intrinsic vessel wall elasticity[2]. There was no departure from our usual technique of percutaneous angioplasty. Although not radiologically apparent, the iliac arteries were grossly calcified and this rigidity may have contributed to disruption of the artery during balloon dilatation.

General factors such as anticoagulation, diabetes mellitus, hypertension and heart valve disease have been implicated as risk factors for the formation of false aneurysm at arterial puncture and catheter entry sites[5] and may have had relevance in this patient.

Acknowledgement

We would like to thank Mr G. E. Heard for his advice and kind permission to report this case.

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Paper accepted 25 October 1986

Correspondence

Oesophageal perforation from home-brewing

Sir

I read with interest the recent report by Hainsworth (*Br J Surg* 1987; 74: 151) describing a case of oesophageal perforation in an amateur brewer caused by the explosion of an unvented commercial aluminium keg. The management of the case raises serious issues in the general care of traumatic oesophageal disruption.

Understandable circumstances led to a significant delay (48 h) in diagnosis, though chest pains, surgical emphysema (two of the components of Mackler's triad, the third being haematemesis) and pneumothorax should have prompted earlier recognition[1]. The use of thin barium rather than water-soluble contrast dye, the performance of an unbuttressed repair, closure of the mediastinal pleura as opposed to wide mediastinal drainage, and the use of absorbable suture material rather than non-absorbable monofilament suture were all invitations to dehiscence of the oesophageal repair in the face of extensive mediastinal and pleural soilage[2–4]. Leakage from the suture line was not surprising. It was surprising to read, however, that the patient was taking oral fluids on the third postoperative day, well before what is generally considered the weakest point of an oesophageal anastomosis or closure; the fifth day[2]. A water-soluble contrast oesophagram would generally be obtained on the seventh to tenth day postoperatively in such a case to confirm the integrity of the repair, with the patient maintained *nil per os* before this time. Suspected leakage would instigate earlier investigation.

Finally, attempted primary repair of the suture line dehiscence on the seventh postoperative day in the face of documented invasive Gram-negative and fungal mediastinal sepsis and poor tissue quality is not to be recommended, and, under these circumstances, the Urschel operation, consisting of oesophageal diversion and exclusion in continuity, wide mediastinal and pleural drainage, and feeding gastrostomy would have been appropriate[5]. Again, the closure leaked, though apparently without untoward sequelae, as it eventually resolved with thoracostomy drainage.

This case must certainly be considered the exception rather than the rule, as the more common outcome would be unremitting intrathoracic sepsis and prolonged oesophagocutaneous leak. While there should no doubt be an admonition for those taken to home-brewing beer, there should also be one for those who deal with traumatic oesophageal disruption in this manner.

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Antibiotic prophylaxis in transurethral prostatectomy

Sir

Having recently completed a study of single, oral dose ciprofloxacin cover for transurethral prostatectomy I was interested in the paper by McEntee *et al.* (*Br J Surg* 1987; 74: 192–4). As the authors admit, the low infection rate in the elective group is not in keeping with most reports. Even when every reasonable effort is made to identify patients with infected urine pre-operatively there usually remain a small number who at the time of resection will have bacteriuria[1]. It is surprising then, that no patient in the elective group was found to have an unsuspected bacteriuria. This contrasts with their high incidence of pre-operative bacteriuria in patients catheterized before operation (80·6 per cent) which is more usually between 40 and 50 per cent[2]. It would be interesting to know in more detail what measures were taken to identify bacteriuria in these groups prior to surgery and entry into the study. These small groups do not appear typical and the observation that the elective group did well without antibiotic cover may be due to problems of selection or a Type II sampling error[3].

In our series, unsuspected bacteriuria discovered immediately prior to operation (19 per cent total; 47 per cent with catheters) carried a greater risk of subsequent infective complications than did pre-operative catheterization alone. Further, patients with sterile urine at the time of operation are still at risk of developing postoperative urinary tract infections[1] and we reduced this incidence significantly with antibiotic cover.

Whilst agreeing that pre-operative catheterization increases the risk of infective complications after transurethral prostatectomy it is only one of the factors involved, some of which are impossible, or impracticable, to identify pre-operatively. I feel it is incorrect, then, to advocate a selective policy when there is increasing evidence that appropriate antibiotic cover should be used in all patients undergoing transurethral prostatectomy[1,4,5].

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Author's reply

Sir

We agree entirely with Mr Shearman's comment that pre-operative catherization is but one of a number of factors predisposing to infective complications following prostatectomy. The high incidence of pre-operative bacteriuria in patients requiring catheterization prior to surgery in this series (80·6 per cent) may be explained by the length of time such catheters were *in situ* before operation (mean peroperative catheter stay 12·3 days). This in turn may be explained by the local management policy for patients admitted in urinary retention—those patients who are fit and fail to void, following trial removal of catheter, are allowed home with catheter *in situ* and re-admitted, usually within 2 weeks, for elective surgery. This policy is also practised in other centres in the United Kingdom and has been found to be more advantageous from an organizational point of view without detriment to patient[1,2].

Patients in the elective surgery group were deliberately chosen because they had no identifiable pre-operative risk factors for infection, including pre-operative bacteriuria — hence the very low incidence of postoperative infection in that group. This re-emphasizes the point that a group of patients exist in whom the risk of infection is so low following prostatectomy that prophylactic antibiotics may not be indicated.

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Ectopic anus in the adult

Sir

Professor Keighley in his article about ectopic anus in the adult (*Br J Surg* 1986; **73**: 974–7) states that patients with high anorectal agenesis are commonly advised to have a permanent stoma. This is certainly not our experience, or that of other paediatric surgical units with which we are familiar. Standard textbooks of paediatric surgery[1] do not support this statement either.

Although the results obtained following pull-through operations for high lesions are not as satisfactory as those following procedures for low lesions it is standard practice to offer a pull-through to almost all babies with rectal agenesis. The only babies in whom a permanent colostomy is usually considered as a first procedure are those with other severe congenital defects (usually cardiac) who have a very limited life expectancy.

Kieswetter and Chang[2] in their analysis of a series of 284 patients with anorectal malformations identified 127 patients with high rectal agenesis. Of these 36 died early in life. At follow-up, continence of the 78 surviving children who could be traced was assessed at between 5 and 30 years. Forty children were found to have a 'good' result (occasional soiling with diarrhoea or unusual physical stress). Twenty had a 'fair' result (occasional soiling or staining with a normal consistency stool with a socially acceptable degree of continence). Only 18 had a 'poor' result (frank incontinence with only occasional control, or a permanent colostomy established after failure of definitive therapy).

This suggests that although a significant number of children have a disappointing result, the outlook is not as gloomy as it may at first seem. Indeed many children gain continence over the years, especially when passing through puberty[3].

It is also reasonable to assume that with recent refinements in operative technique the proportion of poor results should be even lower than quoted above.

A. C. Gordon

The General Infirmary
Leeds
UK

1. Ravitch MM, Welch KJ, Benson CD, Aberdeen E, Randolph JG. *Paediatric Surgery*. 3rd ed. Chicago: Year Book Medical Publishers, Inc. 1979: 1067–9.
2. Kieswetter WB, Chang JHT. Imperforate anus: a five to thirty year follow up perspective. *Progr Pediatr Surg* 1977; **10**: 111–20.
3. Ravitch MM, Welch KJ, Benson CD, Aberdeen E, Randolph JG. *Paediatric Surgery*. 3rd ed. Chicago: Year Book Medical Publishers, Inc. 1979: 1072.

Author's reply

Sir

I accept the optimistic remarks from Messrs Gordon and Spicer, concerning the outcome of patients with high rectal agenesis. It is, of course, possible that my own experience is coloured by patients seen in adult life who have had operations 20 to 30 years ago for high defects. In this age group I have now seen ten patients with severe faecal incontinence despite previous reconstructive surgery all of whom have eventually required an end stoma. Many of these patients have struggled for years attempting to achieve some semblance of continence and the relief achieved by simple stoma construction has been uniformly welcomed. My views of this subject are undoubtedly biased by the referral of patients with impaired incontinence in adult life. Nevertheless many would agree that the functional results of reconstruction for high rectal agenesis is often disappointing.

M. R. B. Keighley

The General Hospital
Birmingham
UK

Recurrent small bowel obstruction associated with piroxicam

Sir

I read with interest the case report by Sukumar on recurrent small bowel obstruction associated with piroxicam (*Br J Surg* 1987; 74: 186). I recently experienced a similar case. A 62-year-old man was admitted with a three-month history of intermittent symptoms of bowel obstruction. He had been taking Rheumox® (azapropazone) for 3 years, an
nifedipine. The obstruction was clearly food induced, clear
relieving it. Subsequent laparotomy revealed small bowel dilat
within 30 cm of the ileocaecal valve and a congenital adhesion
pouch of Douglas which was divided. He appeared
postoperatively and was discharged, but returned 4 weeks late
a recrudescence of symptoms, at which time a small bowel enem
performed. It was entirely normal with no point of obstructi
dilatation.

Further laparotomy revealed dilated small bowel from the
jejunum to 30 cm from the ileocaecal valve with a visibly
transition to intestine of normal diameter distally. On holding up
of dilated bowel we noted the contained fluid did not flow distall
gravity, but appeared to be held up by an intraluminal 'valve'.
pressure on the loop ejected fluid beyond the obstruction, audib
visibly as a fine jet. An enterotomy was performed at this site and a
mucosal 'diaphragm', admitting only a 2 mm probe, was foun
excised.

Exploring the rest of the small bowel with a Foley balloon cath
the lumen revealed a further ten such 'diaphragms'. Resection of m
the small bowel was obviously not advisable over such a length,
treated these diaphragms by multiple stricuroplasties, in wh
longitudinal enterotomy is sewn up transversely.

The patient is well 9 months later, histology showing
mucosal oedema.

I wish to point out the unhelpfulness of the small bowel enem
difficulty in identifying these diaphragms by inspection of the bo
operation, and suggest stricturoplasty with balloon location
treatment of choice, especially when a significant length of bo
involved.

F. Jol

West Suffolk Hospital
Bury St. Edmunds
UK

Oxygen inhalation induced changes in skin

Sir

The article by McCollum, Spence and Walker (*Br J Surg* 1986; **73**:
represents the latest step towards a good idea whose time is c
They note that failure of transcutaneous P_{O_2} (P_{tcO_2}) to resp
oxygen breathing correlates with failure of healing. They m
decline to speculate on a mechanism. An explanation is availa
short, failure of P_{tcO_2} to respond to an elevation of arterial P_{O_2}
says something important about perfusion.

Tissue oxygenation is one aspect of the Fick equation in wl

$$\text{Flow} = \frac{\text{Oxygen consumption}}{\text{Arteriovenous oxygen difference}}$$

Of these three variables, consumption (skin) is constant
arteriovenous oxygen difference can be estimated by tissue oxime
a result, flow can be estimated.

Transcutaneous oximetry measures mean P_{O_2} in the tissue b
the electrode, not arterial P_{O_2}. Heating the electrode assures ma
blood flow under the electrode; thus mean tissue P_{O_2} appr
arterial P_{O_2}. However, if flow is limited, P_{tcO_2} falls because P_{O_2} i
veins falls.

The oxygen extraction ratio of skin in normals is approxi
0·6 volumes per cent (Evans and Naylor[1]). Since this is so lo
transcutaneous oximeter is able to 'solve' the Fick equation for
P_{aO_2} is 100 (torr), venous oxygen tension (P_{vO_2}) (skin) is about
P_{tcO_2} is usually about 80. If P_{aO_2} rises to 300, P_{vO_2} (skin) rises to o
and P_{tcO_2} rises to an intermediate figure. Both P_{tcO_2} and P_{vO_2} are
the steep portion of the haemoglobin–oxygen dissociation cu
poorly perfused feet, P_{aO_2} remains constant, but P_{vO_2} (skin) fa
P_{tcO_2} falls with it into the range of haemoglobin–oxygen assoc
Responsiveness to elevated P_{aO_2} falls because at those levels
oxygen is bound more tightly to haemoglobin.

Though McCollum *et al.* don't specify it, I dare say that in p
with low P_{tcO_2} in the foot, P_{aO_2} can be estimated as equal to P_{tcO}
thigh or chest. P_{tcO_2} in the foot could be substituted for P_{vO_2}. Tl
equation would become

$$\text{Flow (foot)} = \frac{\text{Constant}}{\text{thigh } (C_{aO_2}) - \text{foot } (C_{vO_2})}$$

Unfortunately, the authors do not give haematocrits. As
haematocrits were approximately 40 per cent, the oxygen con
arterial blood of patients (calculated from P_{tcO_2} measured in th

during oxygen breathing) would be 17·5 vol/100 ml blood flow. $C_{\bar{v}O_2}$, similarly calculated from P_{tcO_2} (foot) = 12·8. Thus arteriovenous oxygen difference is 4·7—quite far above the normal of 0·6 reported by Evans and Naylor or the 0·3 calculated from McCollum's data. Therefore, flow in the patients' feet on average was approximately 10 per cent of normals. I suspect that McCollum's data would even more accurately predict failure of healing if calculated in this manner.

Data taken while patients breath oxygen is the most useful because P_{tcO_2} of normals is then elevated so high above the oxyhaemoglobin dissociation curve that skin uses only oxygen transported by plasma. Venous P_{O_2}, therefore, moves up in proportion. However, only well-perfused tissue, with a low oxygen extraction can respond in this manner. Poorly perfused foot skin cannot.

This does not constitute a testimonial to transcutaneous oximetry because we feel that there are better means of measuring perfusion, though probably not for patients such as these with severe peripheral flow deficits. It does, however, constitute an endorsement of the principle that peripheral perfusion can be estimated oximetrically.

T. K. Hunt

Medical Centre
University of California
San Francisco
USA

1. Evans NTS, Taylor PFO. Steady states of oxygen tension in human dermis. *Respiration Physiology* 1966–1967; **2**: 46–60.

Mesh in contaminated abdominal wall defects

Sir

A recent communication (*Br J Surg* 1986; **73**: 415) advocated the use of absorbable synthetic mesh in the semi-open treatment of peritonitis. Others[1] applied absorbable mesh to repair contaminated abdominal wall defects. According to these reports the absorbable mesh need not be removed; it covers the defect until healing occurs either by secondary intention or with the aid of split-thickness skin grafts. Recently we treated a 75-year-old lady with an extensive necrotizing infection of her abdominal wall caused by carcinoma of the transverse colon which perforated into the abdominal wall. At emergency laparotomy the transverse colon was resected *en bloc* with the adherent and necrotic abdominal wall.

The peritoneal cavity was clean and no further planned staged relaparotomies for peritoneal toilet were deemed necessary. It was decided therefore to cover the abdominal wall defect with an absorbable Vicryl mesh instead of the Marlex mesh used by us routinely in similar cases in which repeated abdominal re-entry is necessary. A double layer of Vicryl mesh was sutured to the healthy surrounding fascial edges.

During the stormy first postoperative week about 1 litre of sterile peritoneal fluid was draining daily through the mesh; this and the absence of granulation tissue beneath the mesh was attributed to the low serum albumin levels (19 g/l) resulting in generalized capillary leak and poor tissue healing. On the tenth postoperative day the mesh disintegrated in its centre resulting in complete evisceration of the small bowel. At reoperation remains of the Vicryl mesh were removed and a Marlex mesh was placed covering the entire defect. What sort of synthetic mesh should then be used in the septic abdomen? When subsequent re-explorations are expected the strong and tough Marlex mesh seems superior; it will persist as long as reoperations are necessary; it is easily entered and resutured and it 'accepts' a zip in its midline. When no further relaparotomies are likely to be required an absorbable mesh may possess the above mentioned advantages. It should however be used with caution in the severely ill and catabolic patient. Its early absorption in this situation, when poor tissue healing results in the absence of intraperitoneal adhesions and no bowel agglutination, will lead to evisceration.

Z. Frienkel
M. Schein

J. G. Strijdom Hospital and
University of the Witwatersrand
Johannesburg
South Africa

1. Dayton MT, Buchele BA, Shirazi SS, Hunt LB. Use of an absorbable mesh to repair contaminated abdominal-wall defects. *Arch Surg* 1986; **121**: 954–60.

Infusion cholecystography in acute biliary disease

Sir

I read with interest the report by Gatt and Jantet (*Br J Surg* 1987; **74**: 204–5) and agree with them on the importance of an accurate diagnosis of acute cholecystitis so that early surgical intervention may be planned. In this context their claim of no false positive results from infusion cholecystography is incorrect. Their claim is true for the presence of gallstones, but not for acute cholecystitis (two false positive results out of their twenty-five operated patients). It is important to emphasize that in imaging the biliary tract the detection of gallstones alone is not diagnostic of acute cholecystitis and other criteria must be demonstrated in order to make the diagnosis. In ultrasonography, as mentioned by the authors, secondary signs such as focal gallbladder tenderness, gallbladder wall thickening, and distension are used. Using such strict criteria for diagnosis a very high positive predictive value (greater than 95 per cent) for acute cholecystitis in patients presenting with the clinically suspected condition can be achieved[1].

Infusion cholecystography utilizes similar principles in the diagnosis of acute cholecystitis as HIDA scintigraphy where the biliary excretion of a radiotracer is used to image the biliary tract. In the latter technique acute cholecystitis is diagnosed when the gallbladder is not visualized despite adequate excretion through the biliary tract and a normal result virtually excludes a diagnosis of acute cholecystitis and cystic duct obstruction[2].

It would be interesting to note whether their 20 patients with a 'non-functioning gallbladder' on infusion cholecystography all proved to have acute cholecystitis. Similarly, at least four of their six patients with 'a functioning gallbladder' proved at operation to have acute cholecystitis. How does this fit in with our theories on the pathogenesis of acute calculous cholecystitis?

J. H. Tweedie

University Hospital
Queen's Medical Centre
Nottingham
UK

1. Ralls PW *et al*. Real time sonography in suspected acute cholecystitis. Prospective evaluation of primary and secondary signs. *Radiology* 1985; **155**: 767–71.
2. Hall AW *et al*. The place of hepatobiliary isotope screening in the diagnosis of gallbladder disease. *Br J Surg* 1981; **68**: 85–96.

Author's reply

Sir

We appreciate the interest shown by Mr Tweedie in our article and would entirely agree with his impression that acute cholecystitis was not present in two of twenty-six cases with positive infusion cholecystography. Acute biliary disease was used in preference to acute cholecystitis in the title for this particular reason. However we wish to point out that the criteria used in the original protocol for positive infusion cholecystography, as laid down by Dykes *et al.*[1], included the finding of stones in a functioning gallbladder. In the other four cases with stones in a 'functioning gallbladder' the gallbladders were inflamed and the pathology was confirmed histologically. We can only assume that the obstruction was intermittent.

D. Gatt
G. Jantet

St. Luke's Hospital
G'mangia
Malta

1. Dykes EH, Stewart I, Gray H *et al*. Infusion cholecystography in the early diagnosis of acute gallbladder disease. *Br J Surg* 1984; **71**: 854–5.

Book reviews

Hepatic and Biliary Cancer

H. J. Wanebo. 235 × 155 mm. Pp. 549 + xxxv. Illustrated. 1987. New York: Dekker Inc. $89.75.

This excellently produced multi-author book has chapters covering all of the main topics in hepatic and biliary cancer, each written by a leading authority. Most of the work is from the United States but there are important contributions from England, Japan and France. The book is billed as the first up-to-date, comprehensive source-book of its type, and as providing a broad-based view of this crucial area of research and practice.

It is subdivided into three main sections on cancer of the liver, cancer of the extrahepatic bile ducts and cancer of the gallbladder with a final section on special topics. Although each chapter is of interest and the majority well written, they are essentially individual papers by experts. The overall impression is therefore somewhat disjointed. The ordinary practising surgeon, radiotherapist or oncologist will not find it easy to obtain useful advice to help in the management of an individual patient. It is a pity that clear recommendations on management are not given, other than in the final overview chapter by the Editor.

The primary liver cancer section contains excellent chapters on radiological techniques and angiography for diagnosis. This section occupies 278 pages and surgeons may find the detail excessive. Clear recommendations on management are difficult to find, probably because the treatment of most patients is so disappointing.

There are excellent essays by various experts on extrahepatic bile duct carcinoma which in many instances up-dates their previous reports. Difficulties in management are highlighted as are the disappointing overall results irrespective of the treatment used. The outlook for most patients with cancer of the gallbladder remains dismal.

In the final section there are excellent reviews on the surgical management of liver metastases and the current place of hepatic transplantation for primary carcinoma of the liver. The very limited role of transplantation is highlighted.

The book is an essential acquisition for all major hospital libraries. It is unlikely to be of specific interest to the average practising surgeon, but will be important reading for those with a particular interest in hepatic and biliary cancer.

J. Terblanche

Aids to Operative Surgery

G. J. Poston, 215 × 135 mm. Pp. 214. 1986. Edinburgh: Churchill Livingstone. £7.95.

This latest offering in the 'Aids to' series, will, I am sure, find its way into the hearts and the pockets of many young surgeons coming up to final fellowship. It is a book that many of us would have liked to have written and credit should go to Mr Poston for producing both exhaustive and exhausting lists. However, a word of caution is necessary for the unwary candidate. Although many of the generalizations would be acceptable to most examiners, some of the specific details are no more than personal prejudice and may stimulate unwanted controversy. Indeed there is a potential danger that Lists become learnt by constant recital rather than by theatre experience.

Some of the content is disappointing, for instance the whole of breast surgery is reduced to a single operation — a rather scanty description of simple mastectomy with axillary sampling. Moreover there is too great an emphasis on pre-operative investigations at the expense of operative technique.

At £7.95 the book is excellent value; however, I fear the binding will lead to wider dissemination of the information than is intended. I think the publishers could have left blank space after each procedure for the diligant trainee to add pertinent comments.

M. W. Kissin

Pathology for Surgeons

P. C. H. Watt and R. A. J. Spence. 240 × 160 mm. Pp. 707 + xv. Illustrated. 1986. Bristol: Wright. £35.00.

The authors are to be complimented on writing a comprehensive text covering a wide range of pathology relevant to surgery. The book contains almost 700 pages but is easy to handle and read. It is well set out and gives due reference to the modern approach in certain areas e.g. lymphoma, carcinoma of the stomach and breast. As a summary of pathology for FRCS candidates and undergraduates this book is clear and concise. A good and successful feature is to introduce each chapter with a summary of relevant anatomy and physiology. I liked the diagrams, which are very clear and amplify the text, but some of the photographs illustrating specimens have not reproduced very well.

The publishers suggest that the book will be welcomed by more senior surgeons as a reference book but at this level it is not successful because it presents a didactic view over a very wide field of pathology. Although the book is basically sound, some of the statements are, at least, questionable e.g. 'external fistulae occur in about a quarter of the patients with Crohn's disease'. Nevertheless, it is a good book for the junior surgeon and quite reasonably priced at £35.

P. F. Schofield

Surgical, Diagnostic and Therapeutic Instruments

J. J. Stanek. 220 × 185 mm. Pp. 166 + viii. Illustrated. 1986. Oxford: Blackwell Scientific Publications. £24.50.

This is a small book of 157 pages which is well produced and easy to read. It is divided into three sections—Diagnostic, Therapeutic and Operative instruments. It covers a wide range of topics in each section and, because of the limited space, only a very brief comment is made on each item. The description of each instrument follows a pattern including defintion, explanation, indications for use and technique.

The very shortness of the book limits the number of alternatives that can be shown. There are usually simple drawings of a classical instrument but in some examples these have been omitted spoiling the overall pattern.

The Author suggested his book would be useful to everybody from medical student up to senior surgeons and physicians and radiologists. I think this is incorrect. It is possible that senior medical students and FRCS candidates might like to skim through the pages as means of a quick refresher; however, anyone else interested in buying, using or even comparing instruments, would need to use a much more detailed description. Many large catalogues are available for this purpose.

A. A. Gunn

Current Topics in Surgery. Volume 1

N. Rangabashyam. 250 × 190 mm. Pp. 144. Illustrated. 1986. India: Macmillan India Ltd. Rs 175.00.

It is inevitable that each School of Surgery wishes to publish a selection of essays outlining the current trends in the management of common conditions. The Indian School of Surgery is no exception, having probably a greater need to publish its own material than most, for the conditions which the Indian surgeon encounters differ markedly from those seen in most Western practices. This is well illustrated by the first edition of Current Topics in Surgery in which tuberculosis and amoebiasis take pride of place in the subjects chosen by the Editor. Alas, despite sterling efforts by the Editor, some chapters are pedestrian with a lack of up-to-date references and personal prejudices described but not substantiated by good data collection which is strongly advocated by Aluwihare in his chapter on Rectal Disease. I trust that this will be a forerunner of future editions, and that the Editor will feel able to call upon the younger surgeons who are beginning to stir Indian surgery, and direct it along a more objective and critical path.

R. C. G. Russell

Recent Advances in Orthopaedics. 5

A. Catterall. 240 × 160 mm. Pp. 204 + viii. Illustrated. 1986. Edinburgh: Churchill Livingstone. £30.00.

Number 5 in the orthopaedic series contains 11 chapters, which deal respectively with the fixation of prostheses without cement; the present position of scintigraphy in orthopaedics; avascular necrosis of bone; slipped epiphysis at the proximal end of the femur; 'the problem back'; replacements for joints in the upper limb; pain in the front of the shoulder; clean air and antibiotics in preventing infection; the applications of microsurgery in orthopaedics; and progress in research into the causes of Perthe's disease.

The articles are well written (in spite of numerous typographical errors and spelling mistakes) and serve well their purpose of bringing up to date, in fairly general terms, the orthopaedic surgeon who feels the need to widen his outlook or to delve more deeply into some of the subjects. As well as dealing with technical methods that have added precision to diagnosis and enhanced the prospects or the quality of improvement, the authors have presented the advances in a well balanced way. In the chapters on the back and the shoulder, in particular, the importance of both clinical examination and the personal factors in diagnosis and treatment have received a well-deserved emphasis that is not always accorded them.

P. S. London

Tendon Surgery of the Hand

J. M. Hunter, L. H. Schneider and E. J. Mackin. 284 × 220 mm. Pp. 701. Illustrated. 1987. Oxford: Blackwell Scientific Publications. £80.00.

The book is based on the 1984 Philadelphia tendon symposium which brought together many of the pioneers of tendon surgery in the hand together with those who have contributed much to the subject in recent times. The list of authors is a *Who's Who* of those who have contributed to this special aspect of surgery of the hand.

No facet is neglected and it contains excellent chapters on the basic science as well as the clinical aspects of the primary surgery and reconstruction. The techniques of rehabilitation are described by the latest ancilliaries to aid the hand surgeon, namely, the hand therapists drawn from physiotherapists and occupational therapy disciplines who have done so much to improve the quality of the results and contributed a great deal to the detailed assessment of the hand before and after surgery.

Apart from a comprehensive cover of all aspects of tendon surgery of both the flexors and extensors an interesting feature included is the panel discussions of the various aspects of tendon surgery which synthesize much wise and erudite opinion and the cumulative experience of those taking part.

It is fitting that Guy Pulvertaft of Derby's photograph, with the caption 'a friend and teacher to us all', appears before the foreword. His recent death is a great loss to us all who so valued his wise counsel and incomparable experience. It is a great pity he did not see this volume of which he would have been justly proud for it expresses the 'state of the art' in a difficult subject and unlike most books is right up-to-date.

It will repay anyone who has to deal with injuries or reconstructive surgery of the hand to read it carefully and to savour the content of this excellent book.

B. Helal

Extracorporeal Shock Wave Lithotripsy for Renal Stone Disease

P. Gravenstein. 242 × 160 mm. Pp. 158. Illustrated. 1986. London: Butterworths. £19.50.

Changes in the surgical management of renal stones are occurring so rapidly that it is very difficult for any book to be published before it is out-of-date. The Editors and the Publisher must be congratulated for bringing together a group of experts who, between them, cover the clinical and technical aspects of Extracorporeal Shock Wave Lithotripsy (ESWL) in a comprehensive and authoritative way. The first section, dealing with the historical and the technical background, is easy to read, although some of the physics would be difficult for a clinician to understand fully. Nevertheless, this section provides useful and important information for all those involved in treating patients with lithotripsy. The clinical section includes a chapter on a urological aspect of lithotripsy and more extensive coverage of the specialized anaesthetic techniques that have evolved. A study comparing the anxiety engendered in patients undergoing different methods of stone removal confirms the acceptability of ESWL to patients.

The final section covers the possible complications of ESWL, particularly cardiovascular problems. The safety of the procedure is confirmed and thoughtful prophylactic measures in high risk patients are discussed.

This book will be a useful addition to the library of all urological departments. Urologists in training and those actively involved in lithotripsy might also consider the modest financial outlay to be worthwhile.

H. Whitfield

Manual of Vascular Access Procedures

T. Matsumoto, S. Simonian and A. M. Kholoussy. 150 × 225 mm. Pp. 118. Illustrated. 1987. Hemel Hempstead: Simon and Schuster. £32.05.

If anyone doubts that English and American are two different languages, this book should convince them. It gives the firm impression of having been dictated in American rather than written in English and this unfortunately spoils the impact of the extensive and detailed coverage of access procedures for haemodialysis, peritoneal dialysis and chemotherapy which it contains. 'This is versus the 7 times more efficient normal kidneys' (page 3) is but one example of the tortured grammar and confused (and confusing) punctuation that make the book so uncomfortable to read. This is a shame, because contained within only 118 pages are descriptions of a wide range of surgical techniques. Section one covers vascular access for acute and chronic dialysis and procedures for peritoneal dialysis. Many of the descriptions are detailed and excellent, but there are aberrations—for example Thomas and Allen-Brown shunts (rarely used in this country) are given great emphasis, whilst the more common ankle shunt merits only half a line, which incorrectly suggests the use of the short saphenous vein. The description on page 29 of a side-to-side anastomosis is also wrong. Section two covers long term intravascular access for parenteral nutrition and chemotherapy, and describes Hickman and Broviac catheters, implantable systems such as the Port-A-Cath, and subcutaneous infusion pumps. As before, the information is good, the text clumsy, and the line drawings excellent. The photographs, unfortunately, are unhelpful. I wouldn't buy the book, but I would be happy for my registrars to read it were it to be in the library.

C. Rudge

Notices and announcements

Meetings

19–24 July 1987
Mechanisms of Carcinogenesis
Saxtons River, Vermont, USA
Information: Robert W. Krauss, Executive Director, FASEB, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

26–31 July 1987
Biology of Tumor Metastases
Saxtons River, Vermont, USA
Information: Robert W. Krauss, Executive Director, FASEB, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

9–14 August 1987
Energy Regulation of Energy Balance
Saxtons River, Vermont, USA
Information: Robert W. Krauss, Executive Director, FASEB, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

16–21 August 1987
17th World Congress of the Society of Orthopaedic and Traumatological Surgery
Munich, FRG
Information: Dr W. Baur, Orthopädische Klinik, D-8501 Schwarzenbruck/Nuremberg, FRG

24–28 August 1987
The Prevention and Management of Organ Failure
London, UK
Information: The Conference Organizer, Critical Care '87, BJHM, Battersea Business Centre, 103–109 Lavender Hill, London SW11 5QL, UK

31 August–4 September 1987
Surgical Efficiency and Economy
Lund, Sweden
Information: Professor S. Bengmark–SEE, Box 5121, S-220 05 Lund 5, Sweden

4–6 September 1987
IMLS. Quality Assurance Symposium
Liverpool, UK
Information: Mr D. Kilshaw, Department of Pathology, Arrowe Park Hospital, Arrowe Park Road, Upton, Wirral, Merseyside L49 5LN, UK

6–8 September 1987
An Introduction to Laser Surgery
Sheffield, UK
Information: Mrs V. M. Coomer, Regional Conference Centre, Lodge Moor Hospital, Sheffield S10 4LH, UK

6–10 September 1987
VIth World Congress of the International Society for Artificial Organs and XIVth Congress of the European Society for Artificial Organs
Munich, FRG
Information: Organizing Secretariat, A. Kössl, Sophienstrasse 1, D-8000 Munich 2, FRG

9–11 September 1987
Clinical Controversies in Inflammatory Bowel Diseases
Bologna, Italy
Information: Organizing Secretariat, SO.GE.PA.CO. Spa. piazza Constituzione, 5/c, 40128, Bologna, Italy

14–18 September 1987
International Meeting on Tumour Necrosis Factor and Related Cytokinins
Heidelberg, FRG
Information: Professor H. Kirchner, Cancer Research Centre, Institute of Virus Research, Im Neuenheimer Feld, 6900 Heidelberg, FRG

15–18 September 1987
The British Society of Gastroenterology Jubilee Meeting
London, UK
Information: The Administrative Secretary, The British Society of Gastroenterology, 3 St Andrew's Place, Regent's Park, London NW1 4LB, UK

18–22 September 1987
69th Annual Meeting of the American Association of Oral and Maxillofacial Surgeons
San Francisco, California, USA
Information: K. H. Hajduk, 211 East Chicago Avenue, Suite 930, Chicago, Illinois 60611, USA

20–25 September 1987
32nd World Congress of Surgery
Sydney, Australia
Information: Secretariat, GPO Box 2609, Sydney, NSW Australia 2001

5th October 1987
An International Symposium of Second Generation Lithotripsy for Urologists and Hospital Administrators
London, UK
Information: Ms Pauline Sleight, BDI Conferences Ltd, Kensington Business Centre, 9–11 Kensington High Street, London W8 5NP, UK

11–16 October 1987
Annual Clinical Congress of the American College of Surgeons
San Francisco, California, USA
Information: American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

15–17 October 1987
Fourth Meeting of the European Chapter of the International Union of Angiology
Brussels, Belgium
Information: Madame D. Shanni, Administrative Secretariat, ECCO, Rue Vilain XIIII, 17a, B-1050 Brussels, Belgium

18–24 October 1987
Recent Advances in Pancreaticobiliary Surgery
Glasgow, UK
Information: Professor D. C. Carter, University Department of Surgery, Queen Elizabeth Building, Royal Infirmary, Glasgow G31 2ER, UK

22–23 October 1987
First British Symposium on Surgical Stapling
Manchester, UK
Information: Conference Coordinates, Confer House, 69 Kingston Road, New Malden, Surrey KT3 3PB

24–25 October 1987
Autumn '87 Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, c/o Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

30 October–3 November 1987
8th Asian Congress of Thoracic and Cardiovascular Surgery
Singapore
Information: Dr N. C. Tan, Academy of Medicine, Singapore, 4-A College Road, Singapore 0316

1–6 November 1987
Progress in Cancer Management: Radiotherapy and Chemotherapy
London, UK
Information: Courses Department, The British Council, 65 Davies Street, London, W1Y 2AA, UK

Notices

Volunteers needed for 3–6 weeks surgical appointments in overseas Mission Hospitals. Please contact: Mr M. W. Flowers, Accident and Emergency, General Infirmary, Great George Street, Leeds LS1 3EX.